The Development of Percutaneous Isolated Hepatic Perfusion to Deliver Dose Intensive Treatment to the Liver

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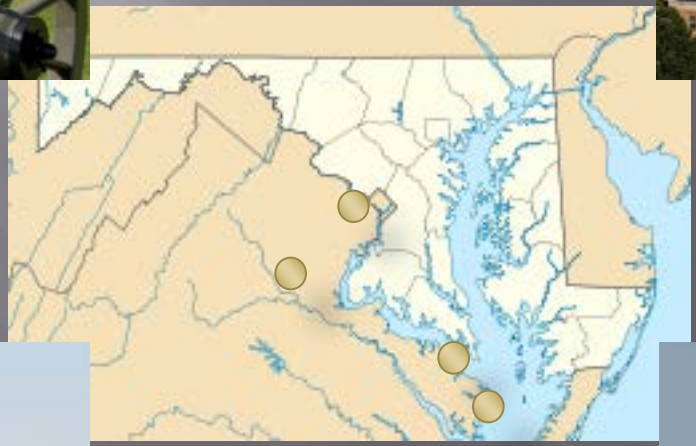
Maryland Environs



Baltimore

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Diffuse Liver Metastases: A Major Clinical Problem

- **Unresectable cancers (primary or metastatic) confined to liver are a significant clinical problem:**
  - **Colorectal cancer: 35,000/yr**
  - **HCC/cholangiocarcinoma: 20,500/yr**
  - **Ocular melanoma: 2,500/yr**
  - **Neuroendocrine tumors: 3,000/yr**
  - **Other histologies**

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

- **Morbidity and mortality in this setting is most frequently a consequence of disease progression in the liver.**

- **Effective control of isolated diffuse metastases to the liver is a significant clinical challenge**

Hepatic Arterial Infusional Therapies: Advantageous Features

- Intra-arterial delivery of therapeutic agents (versus portal venous system) will be *preferentially delivered to metastases*
- *Dose escalation* of therapeutic agents is possible
  - Normal tissue tolerance of the perfused organ is higher
  - Infused agent should have a broad non-specific mechanism of action
  - Melphalan has a broad spectrum of activity with dose levels achieved during PHP
- *Control of systemic exposure* is possible
  - First pass effect (FUDR)
  - Sequestration in the liver (TACE, SIRS)
  - Physical isolation
  - Filtration
- *Systemic toxicities can be easily diagnosed and managed*; comparable to the toxicities seen with commonly used systemic chemotherapeutic agents
- Potentially provides treatment to the *entire organ*
- Provides opportunity to use *novel agents*

Evolving Approach to Cancer Therapy

Old Linear Model of Cancer Care

Surgery

Chemotherapy

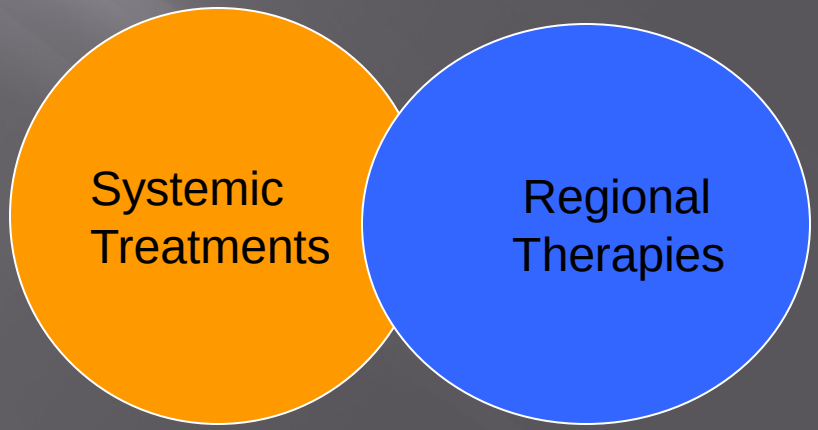
Radiation

Palliation

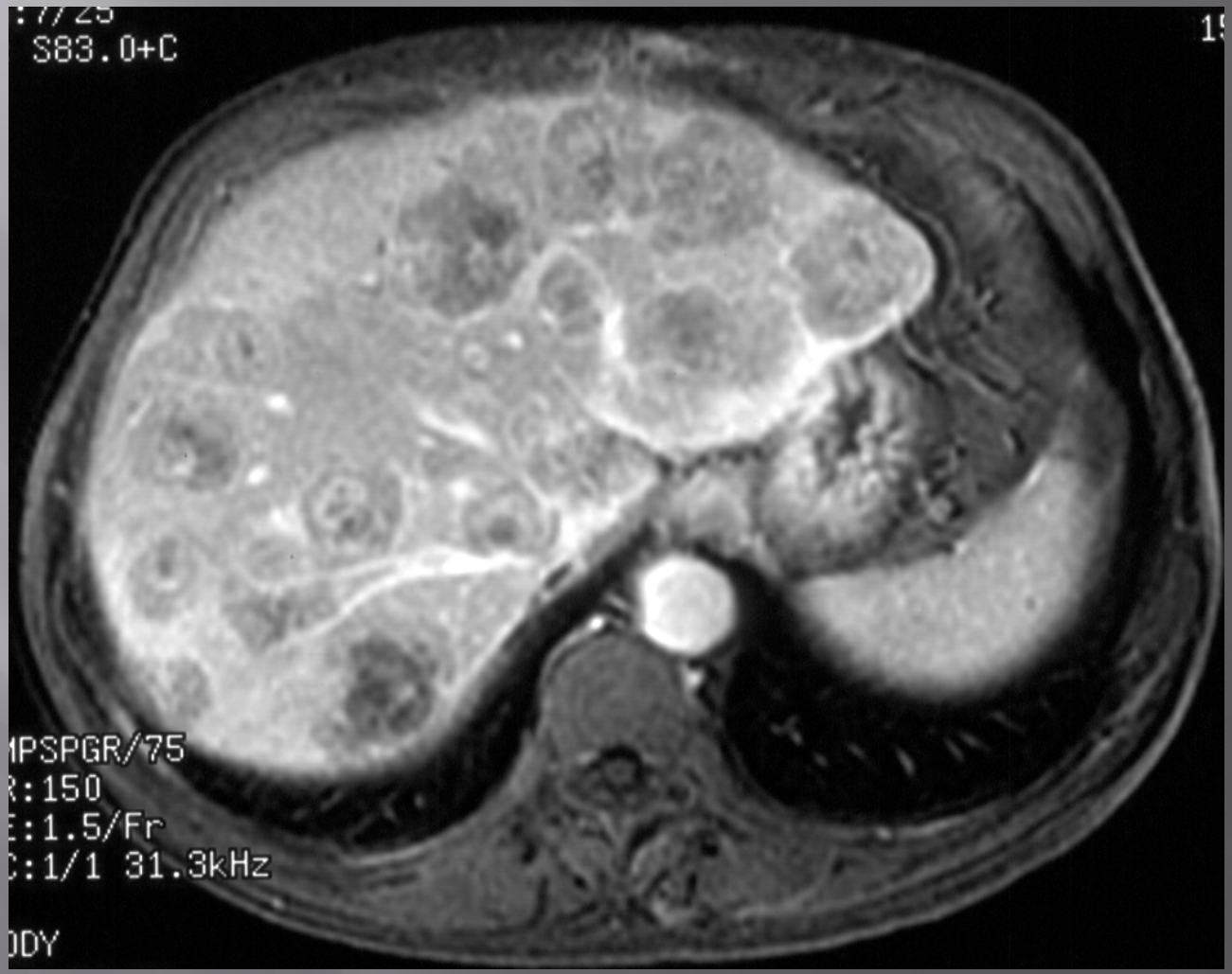
Integrated Care Model

Interdisciplinary Treatment Planning

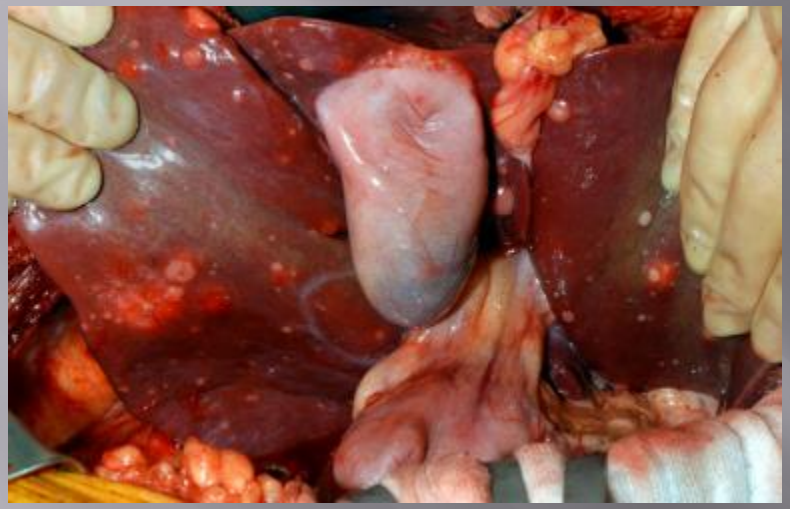
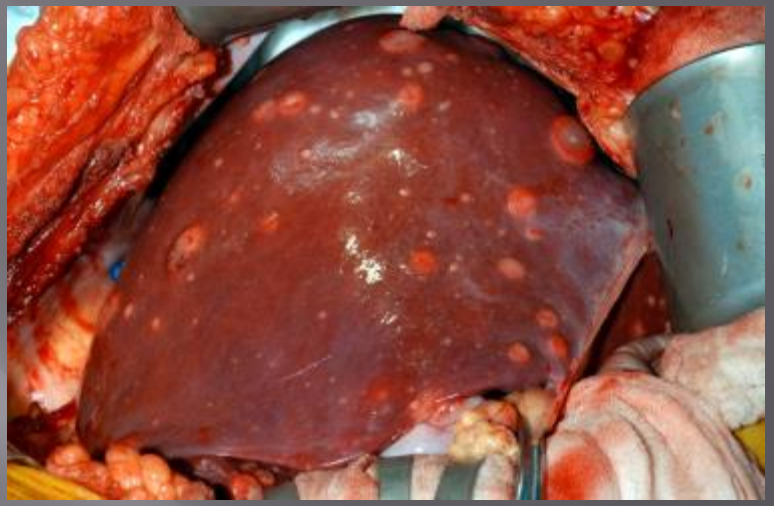
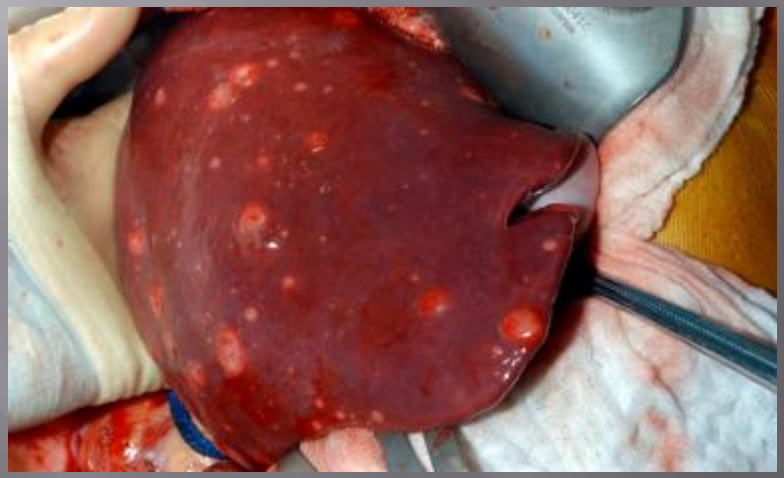
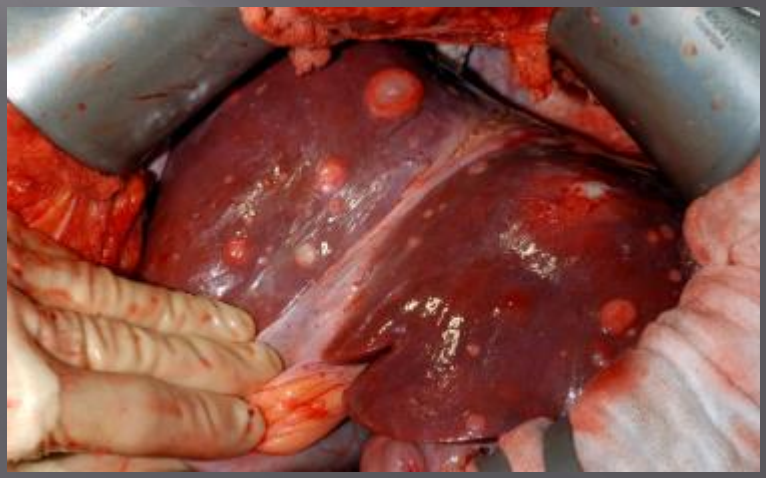
Disease Biology



Example of Extensive Hepatic Colorectal Metastases

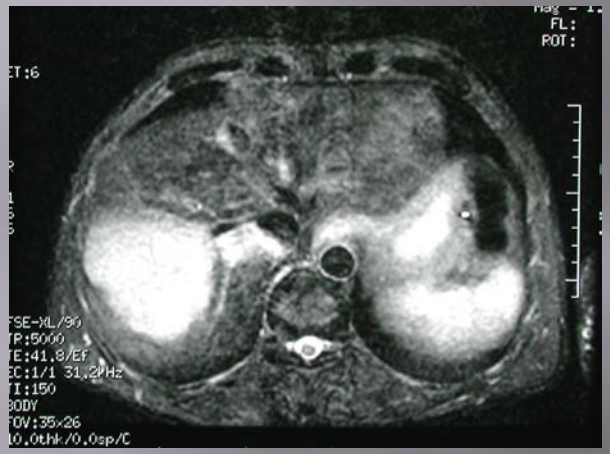


Diffuse Hepatic Neuroendocrine Cancer Metastases

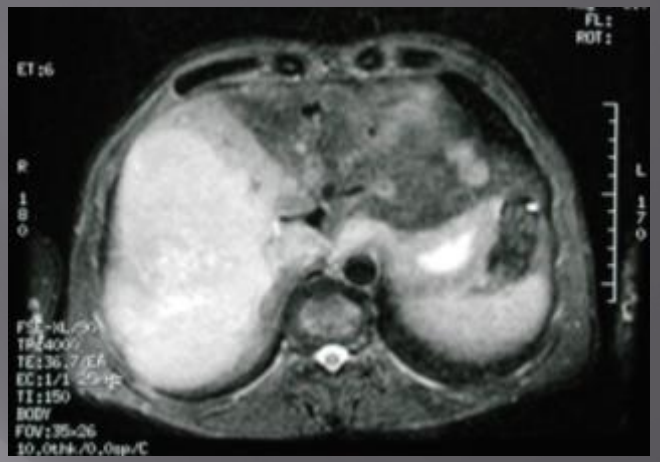





Characteristics of Metastatic OM to Liver

Rapid hepatic progression



75 d interval



Diffuse pattern of metastatic spread

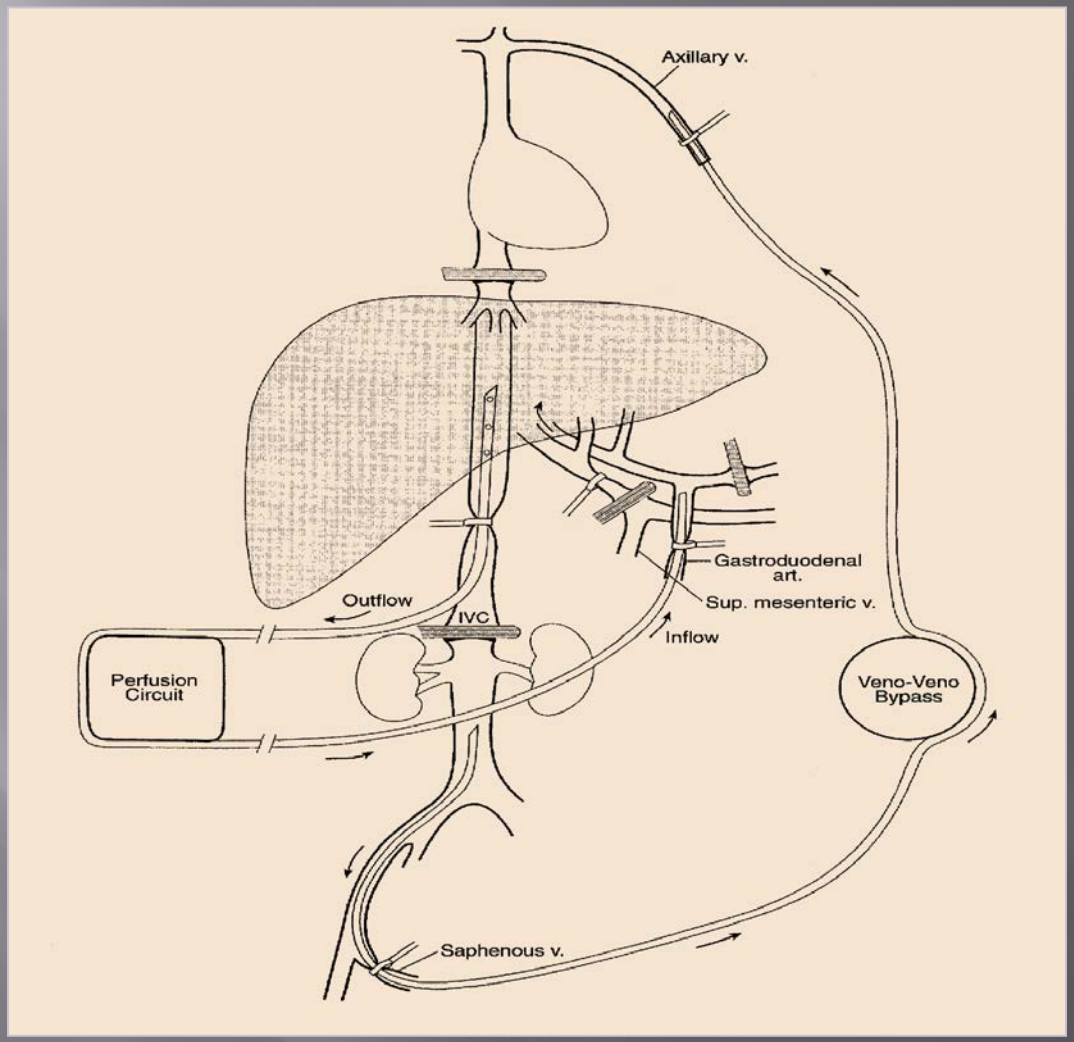
Historical Perspectives in Organ Perfusion

- First clinical application was isolated limb perfusion by Creech and Krementz at Tulane (1950's)
- First series of isolated hepatic perfusion for the treatment of cancer were performed at Roswell Park by Dr. Robert Ausman (1959)
- First successful ex-vivo organ perfusion was performed by Alexis Carrel (1930's) with his collaborator…

Charles Lindbergh

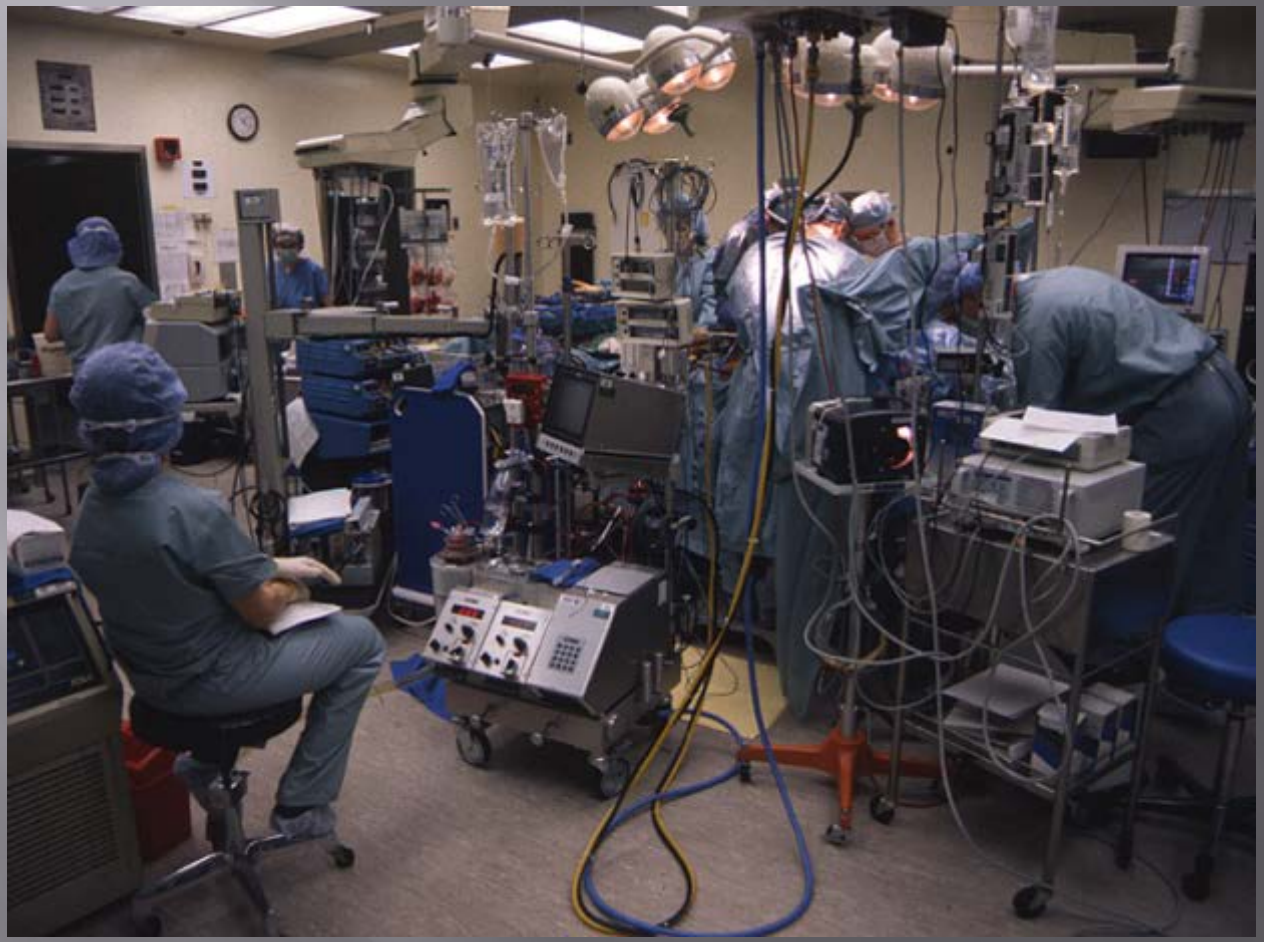
- First successful solo trans-Atlantic flight in 1927
- Originally from Little Falls, Minnesota
- Naturally gifted mechanic, studied engineering at University of Wisconsin
- Was fascinated by Dr. Carrel's work in organ preservation
- Collaborated with him and built the first perfusion machine capable of maintaining organ viability ex-vivo

Surgical Isolated Hepatic Perfusion (IHP)



Alexander HR, The Cancer Journal, Vol 16 No.2, 2010

Operative Set Up



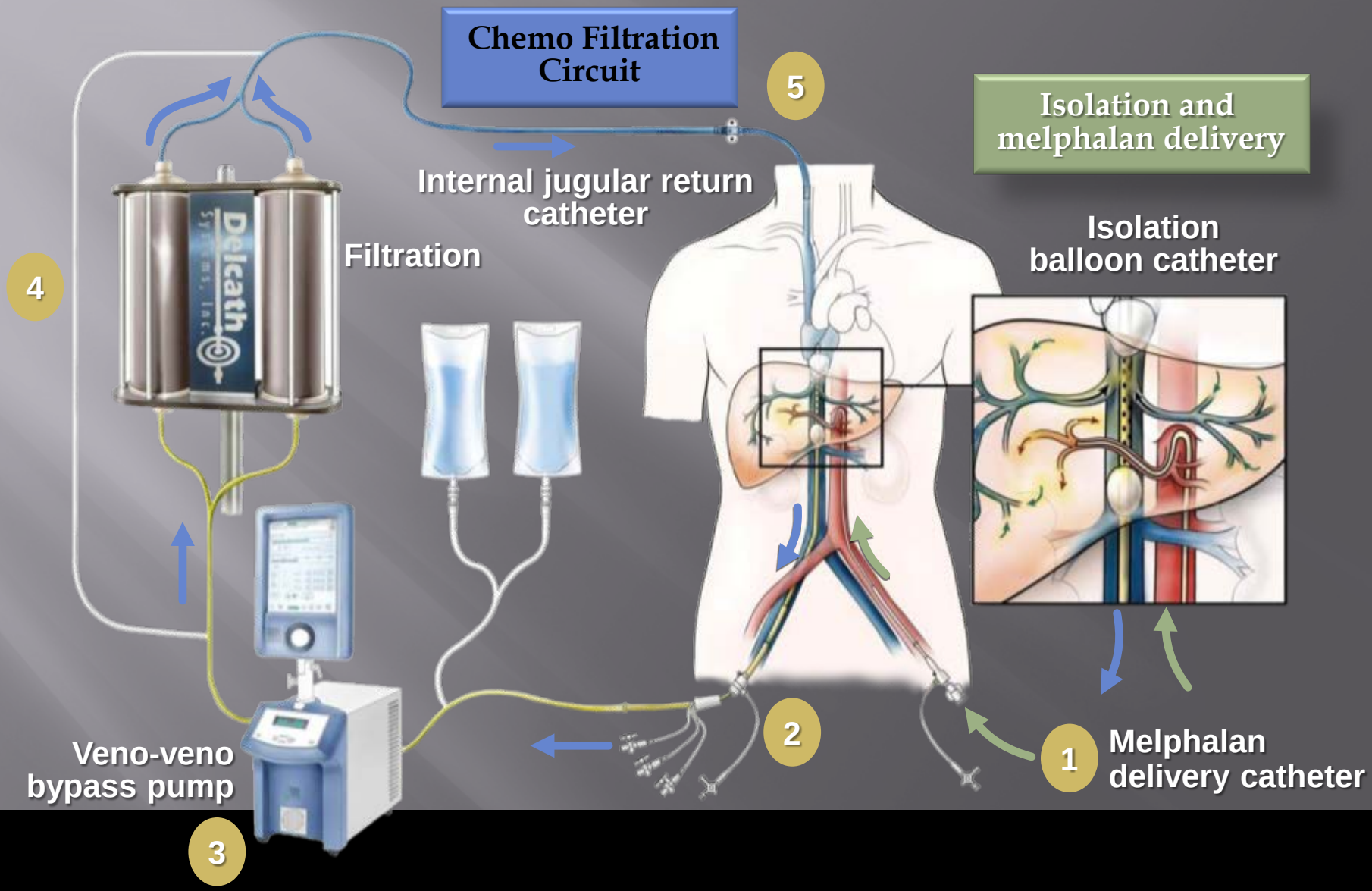
Rationale for PHP as Treatment for Patients with Liver Metastases

- **Melphalan alkylating agent with steep dose response**
  - **Established efficacy against melanoma and other cancers via regional perfusion**
- **Allows intensive dose delivery to the liver via hepatic artery**
  - **Arterial chemotherapy administration provides preferential tumor delivery**
  - **Treats the entire tumor burdened organ**
- **Limits systemic drug exposure by extra-corporeal filtration**
  - **Hepatic venous outflow can be isolated via a double balloon catheter**
- **Minimally invasive procedure**
  - **Uses standard interventional radiology techniques**
  - **Repeatable**

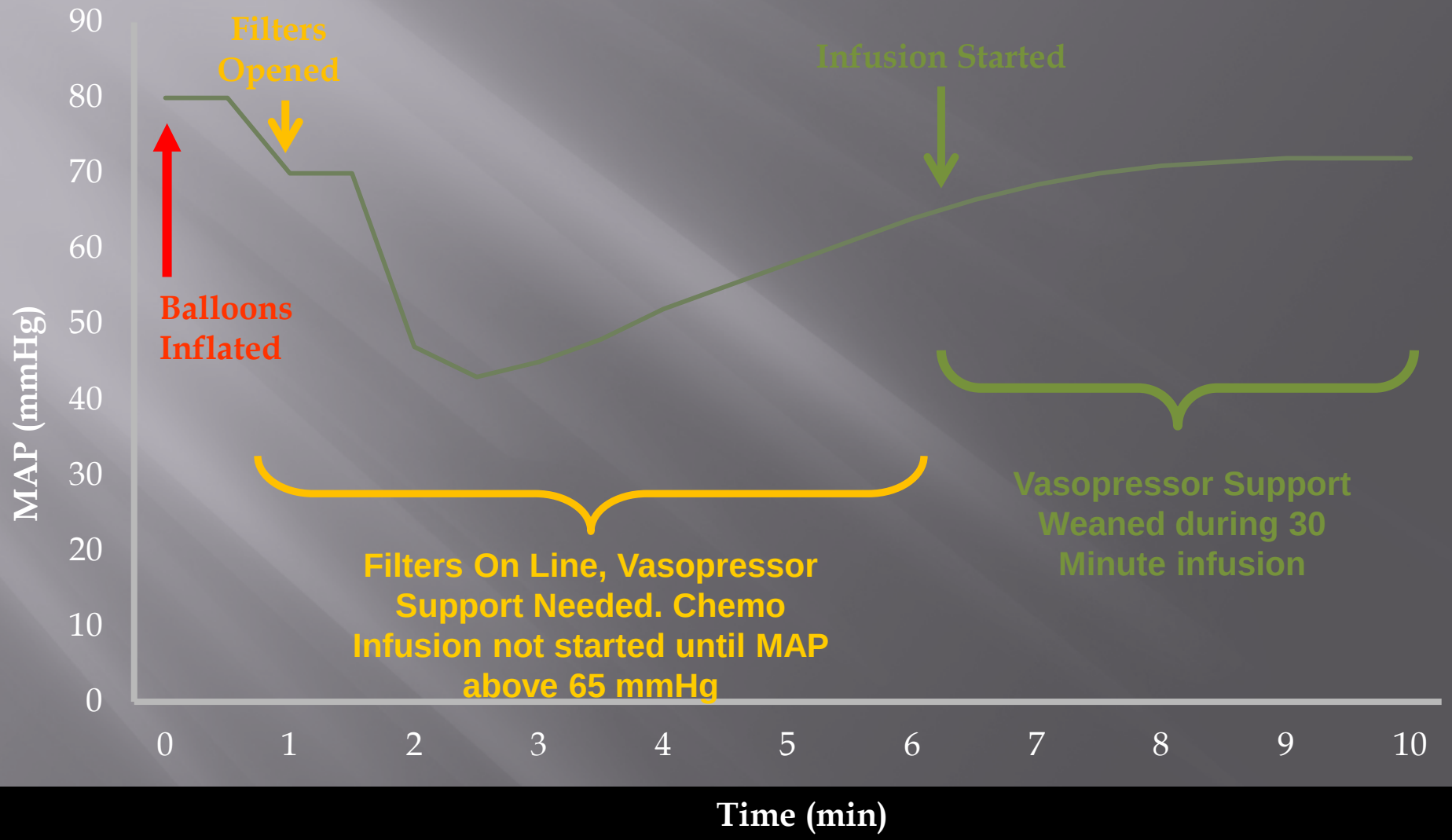
Pre-Procedural Patient Selection

- Ensure adequate cardiac, hepatic, hematologic and renal function
- Complete CT/ MRI, pelvis, abdomen, chest, brain
- Exclude hepatic failure and portal hypertension
- Screen for prior biliary vascular surgery
- Visceral imaging and pre-embolization
- Screen for predisposition for bleeding
- Hypersensitivity to melphalan

PHP Procedure



Management of Blood Pressure During Procedure



Patient Support During PHP Procedure

- **Procedure over 3 hours**
  - Establish venous and arterial access
  - Heparinization
  - Liver isolation with extracorporeal circuit initiation
    - Vasopressors for hypotension
  - Filtration
    - Vasopressors for hypotension
  - 30 minute hepatic intra-arterial Melphalan infusion
    - Nitroglycerin for hepatic artery spasm
  - 30 minute washout period
  - Filters and circuit off
  - Anti-coagulation reversal
- **Recovery and ICU for 24 hours**
  - Correct coagulopathy and anemia
  - Correct electrolyte
  - Monitor VS

Coordination of Treatment Team Responsibilities: Optimize Outcome and Minimize Risk

Team Member	Roles and Responsibilities
Interventional Radiologist	Training, coordination and communication
Surgical Oncologist (or Medical Oncologist)	Patient's complete management
Anesthesiologist	Sedation, analgesia, hemodynamic support
Perfusionist	Establishing, monitoring and controlling the extracorporeal circuit
Certified HCP for Chemotherapy Delivery	Melphalan administration
Interventional Radiology Staff (RN/RT)	Assists in procedure and imaging
Pharmacist	Preparation of melphalan

NCI Phase I Study Design (01-C-0215)

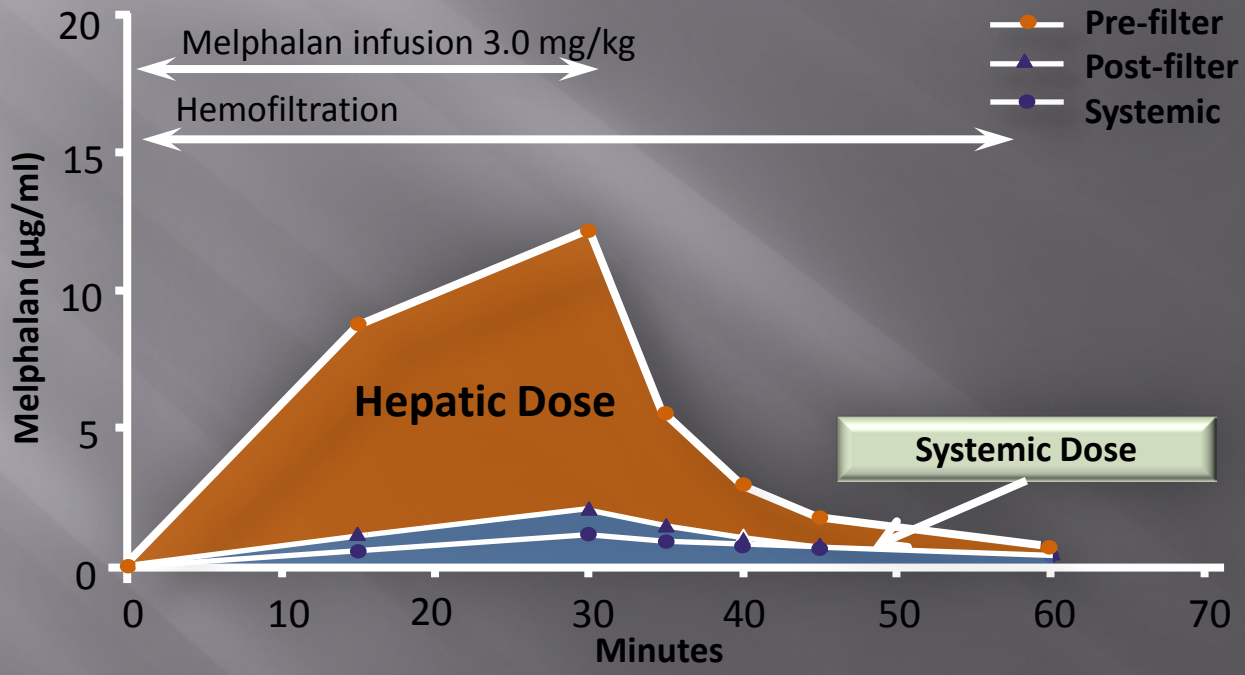
Trial Design	**Open-label, single-center, multiple-ascending-dose**
Patients	**Unresectable primary or metastatic hepatic malignancies from a non-liver primary site**
Objectives	**To determine DLT/MTD, toxicities, PK**
Doses	**2.0-3.5 mg/kg ideal body weight** ▫ **0.5 mg/kg increments** ▫ **Starting dose based on open surgical isolated perfusion experience**
Cycle Length	**4-week cycles for a maximum of 4 cycles**

Phase I Findings

- Defined MTD as 3.0 mg/kg
- DLTs were due to bone marrow suppression
  - No deaths on study
- Clinically meaningful hepatic responses in ocular melanoma including 3 radiographic complete responses

Concentrated Chemotherapy to the Liver

Deliver concentrated chemotherapy directly to the liver with limited systemic exposure



Activity in Phase I Study

Hepatic Objective Response	Ocular Melanoma (N=12)	Cutaneous Melanoma (N=3)	Other Tumor Type (N=19)
Response	4 (33.3)	0	0
Complete Response	3 (25.0)	0	0
Partial Response	1 (8.3)	0	0
Stable Disease	3 (25.0)	1 (33.3)	7 (36.8)
hPFS (median, months)	8.9	2.1	2.9

Phase II Study Design

Design

- Prospective study
- Performed at National Cancer Institute, Bethesda, MD
- Predefined analysis of patient subgroup with neuroendocrine tumors was performed

Patients

- Unresectable hepatic metastases, with limited extrahepatic disease

Treatment

- Melphalan 2.5–3.0 mg/kg delivered by CS-PHP
- Up to 4 treatments planned every 4–5 weeks

Efficacy evaluation

- Primary endpoint – hepatic response rate (RECIST)

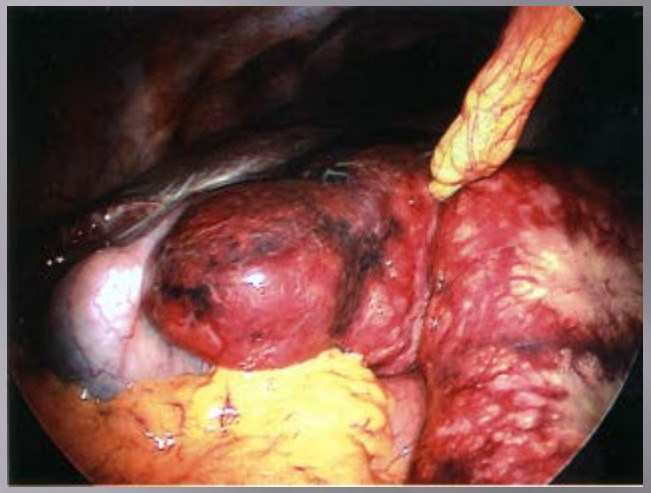
Pingpank J, et al. American Hepato-Pancreato-Biliary Association Annual Meeting 2008
Hughes MS, et al. Proc ECCO-ESMO 2011 (abstr #6621)

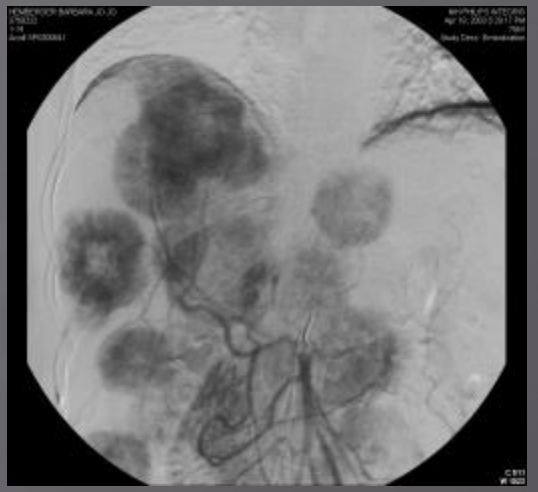
Efficacy Analysis

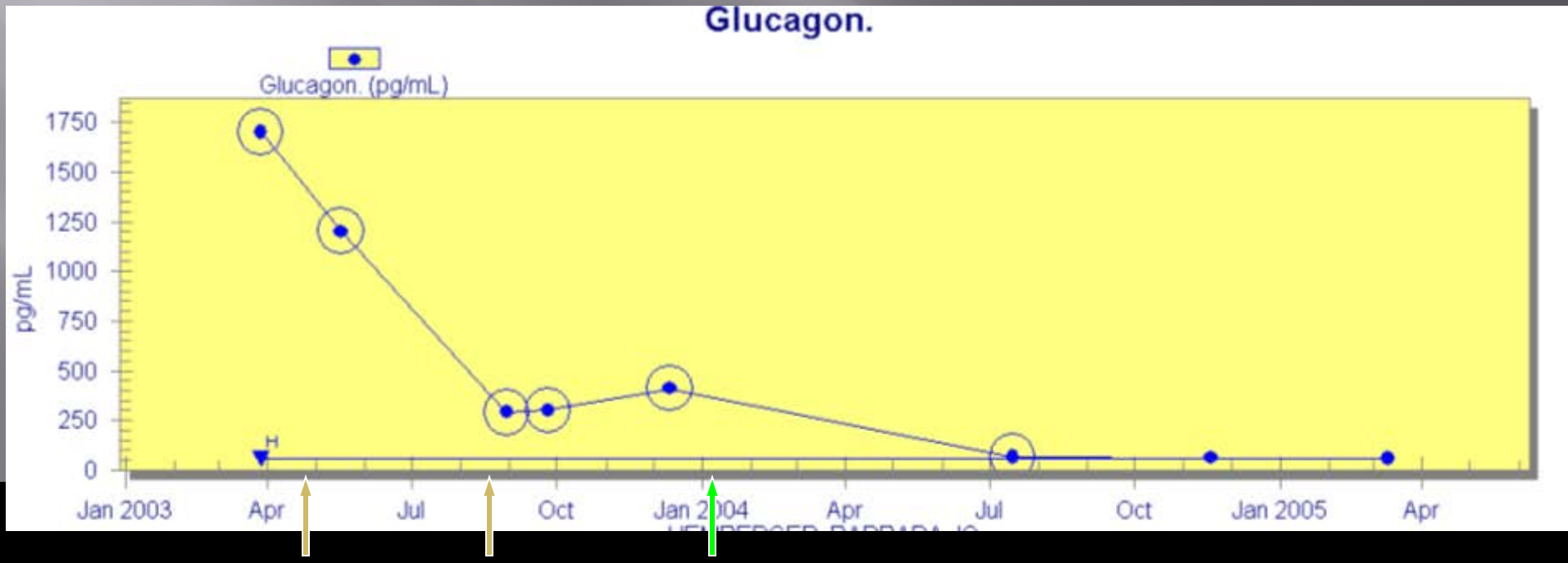
Parameter	No. of patients (N=24)
Overall response rate (intention-to-treat), n	14 (58%)
Complete response	1
Partial response	13
Stable disease	4
Progressive disease	2
Not evaluable*	4
Median hepatic progression-free survival, months	15.5
Median overall survival, months	30.4

*Toxicity, incomplete regimen or transplant.

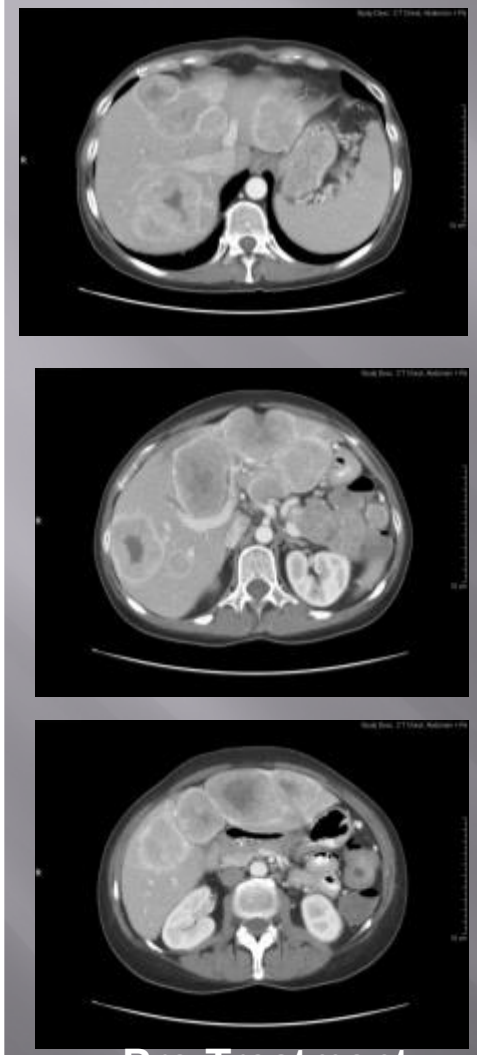
Metastatic Glucagonoma





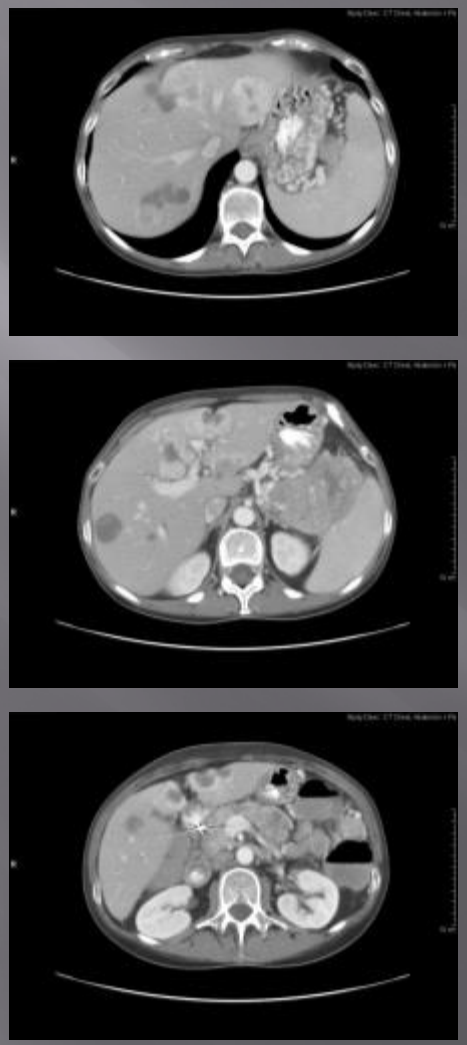


Metastatic Glucagonoma



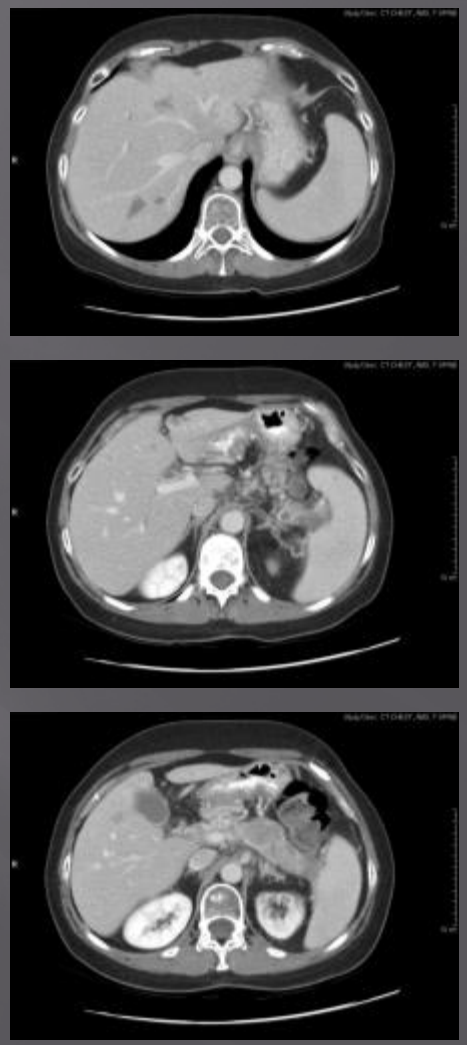
Pre-Treatment

April 2003



Post-PHP x 2

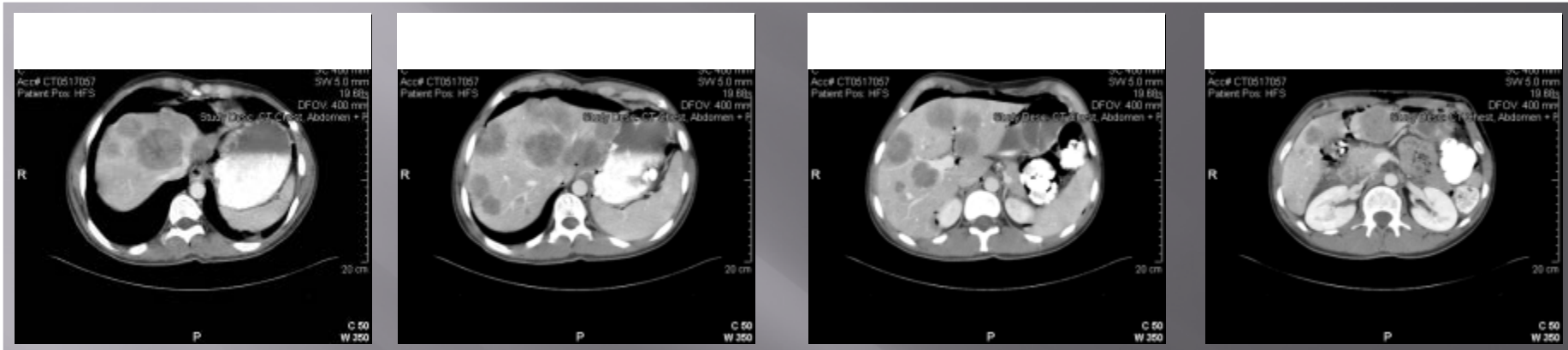
November 2003



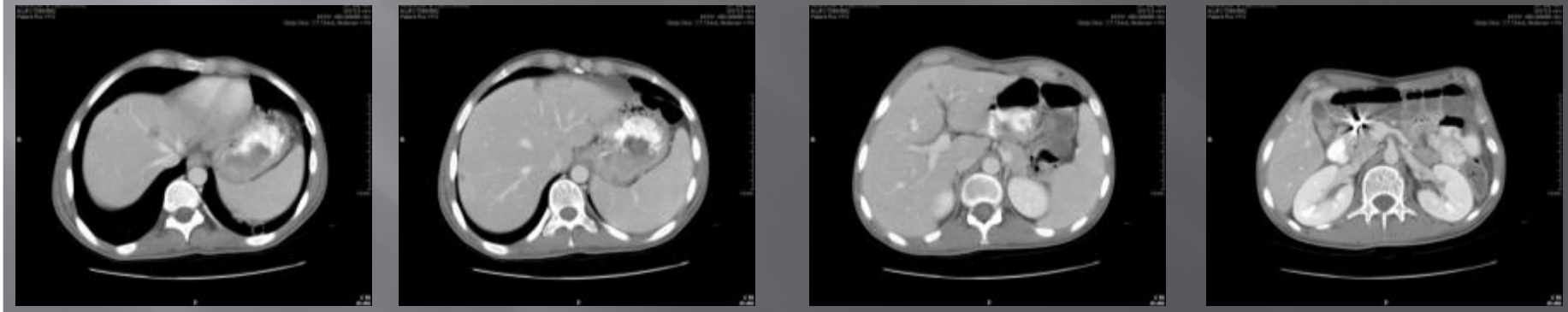
Follow-up (22m)

March 2005

Metastatic Poorly-Differentiated Neuroendocrine Tumor



Pre-PHP: December, 2005



Post-PHP#2: April, 2006

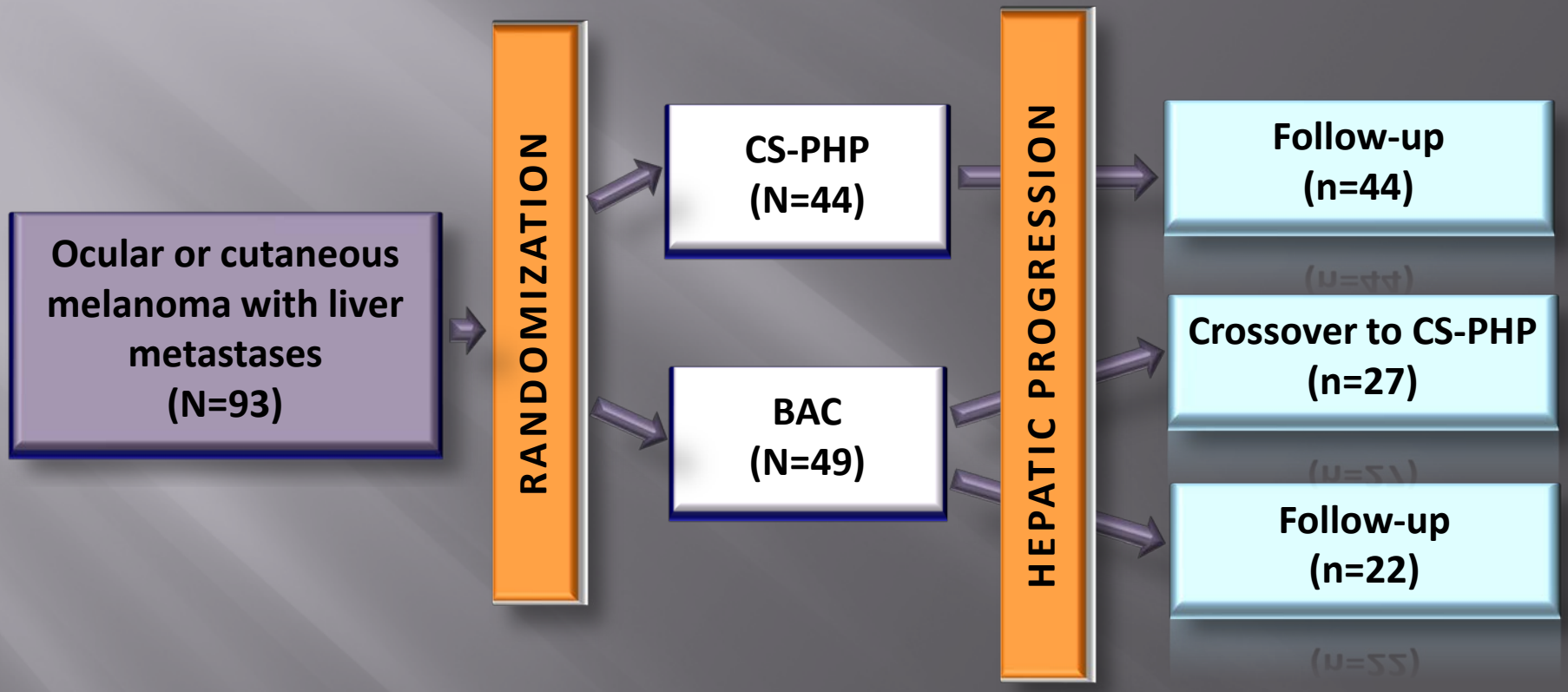
Phase III Study design

- Design
  - Randomized, multicenter phase 3 study
  - PHP *vs* best alternative care (BAC)
- Patients
  - Ocular or cutaneous metastatic melanoma predominantly in the liver parenchyma with limited extra-hepatic disease
- Study endpoints
  - Primary
    - Hepatic progression-free survival (hPFS) (RECIST)
  - Secondary
    - Hepatic objective response rate
    - Overall survival
    - Safety

Phase III Study Treatments

- PHP with melphalan
  - 3.0 mg/kg as a 30-minute intra-arterial infusion
  - An additional 30 minutes of extracorporeal filtration at end of infusion (washout)
  - Under general anesthesia
  - Up to 6 treatments repeated every 4–8 weeks
- Best alternative care (BAC)
  - Investigator's choice of systemic, regional or other appropriate therapy
  - Crossover to CS-PHP permitted after hepatic progression (if patients still met eligibility criteria)

Treatment Flowchart



Baseline Characteristics

	Category	PHP N=44	BAC N=49	P value
Age (years)	Mean	55	55	NS
Gender	Male	23 (52%)	22 (45%)	NS
	Female	21 (48%)	27 (55%)	
Race	White	44 (100%)	48 (98%)	NS
	Non-White	0 (0%)	1 (2%)	
ECOG performance status	Missing	3 (7%)	4 (8%)	NS
	0	37 (84%)	42 (86%)	
	1	4 (9%)	3 (6%)	
Primary tumor	Ocular	39 (89%)	43 (88%)	NS
	Cutaneous	5 (11%)	6 (12%)	
Previous therapy	Radiation (primary tumor)	23 (52%)	24 (49%)	NS
	Chemotherapy	7 (16%)	6 (12%)	
	Immunotherapy	6 (14%)	7 (14%)	
	Image-directed local therapy	2 (5%)	3 (6%)	

ECOG, Eastern Cooperative Oncology Group.
Intent-to-treat population.

Efficacy Analysis

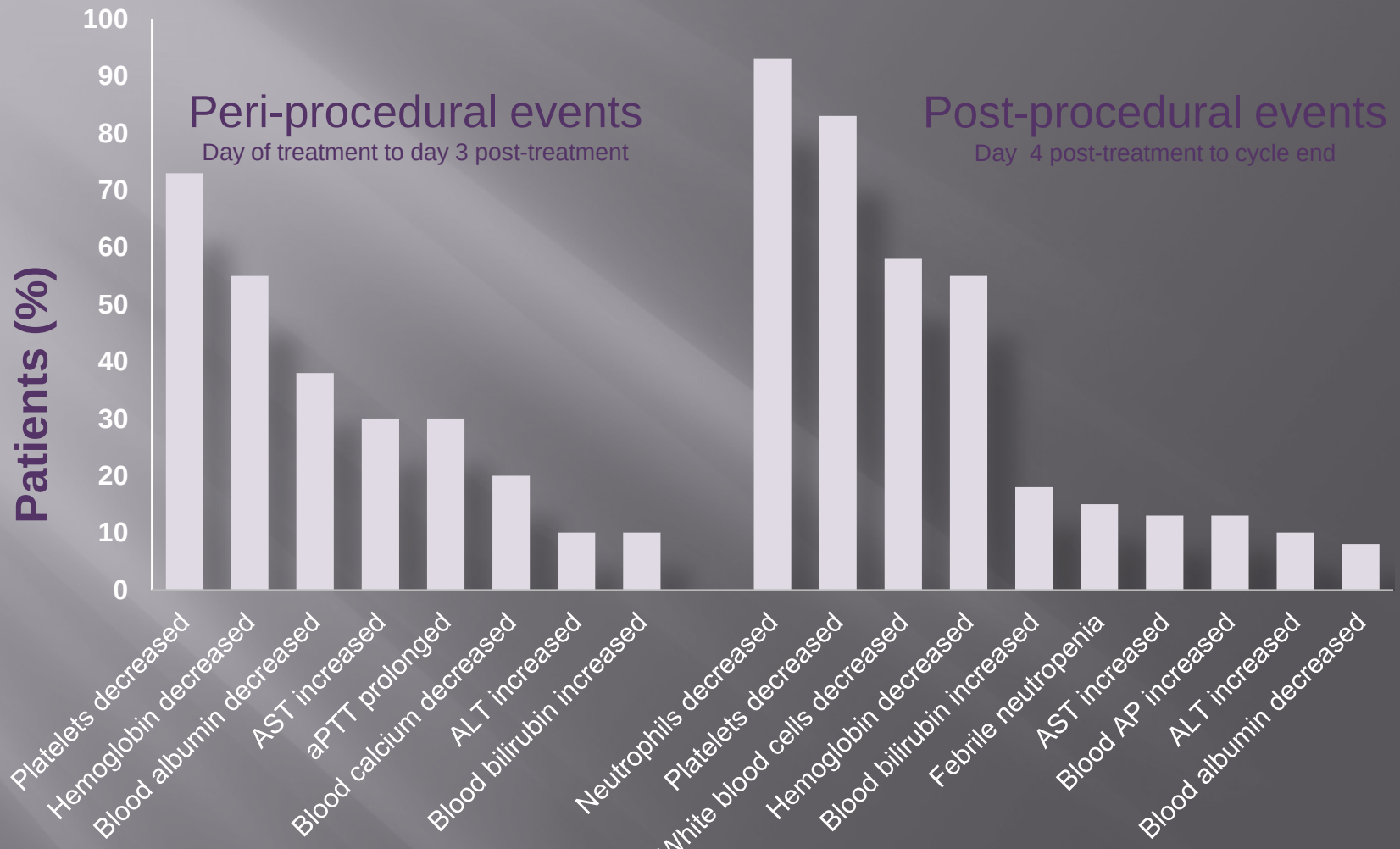
Endpoint	PHP (N=44)	BAC (N=49)	HR (95% CI)	P value
Primary endpoint (investigator-assessed)				
Median hPFS, months	8.0	1.6	0.30 (0.18–0.50)	<0.0001
Secondary endpoints				
Median overall survival, months	9.7	9.9	0.92 (0.52–1.62)	NS
Median progression-free survival, months	6.1	1.5	0.40 (0.25–0.65)	<0.001
Objective response rate, n (%)	15 (34)	1 (2)	–	<0.001

Exploratory Analysis

Endpoint	PHP randomized (N=44)	BAC only (N=22)	BAC-to-PHP crossover (N=27)
Median overall survival, months	9.7	4.1	13.1

P=0.0117

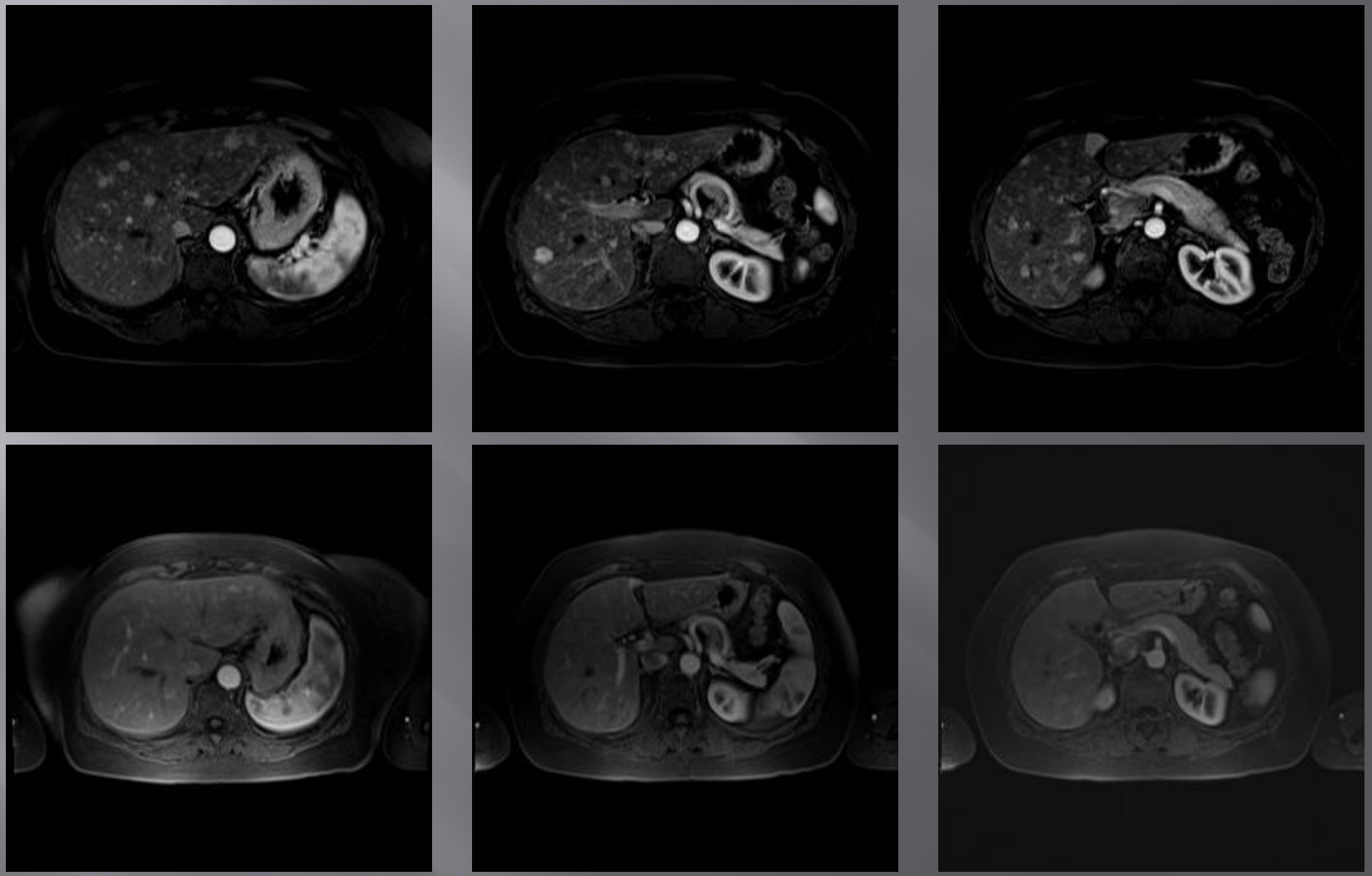
PHP Grade 3/4 Toxicities



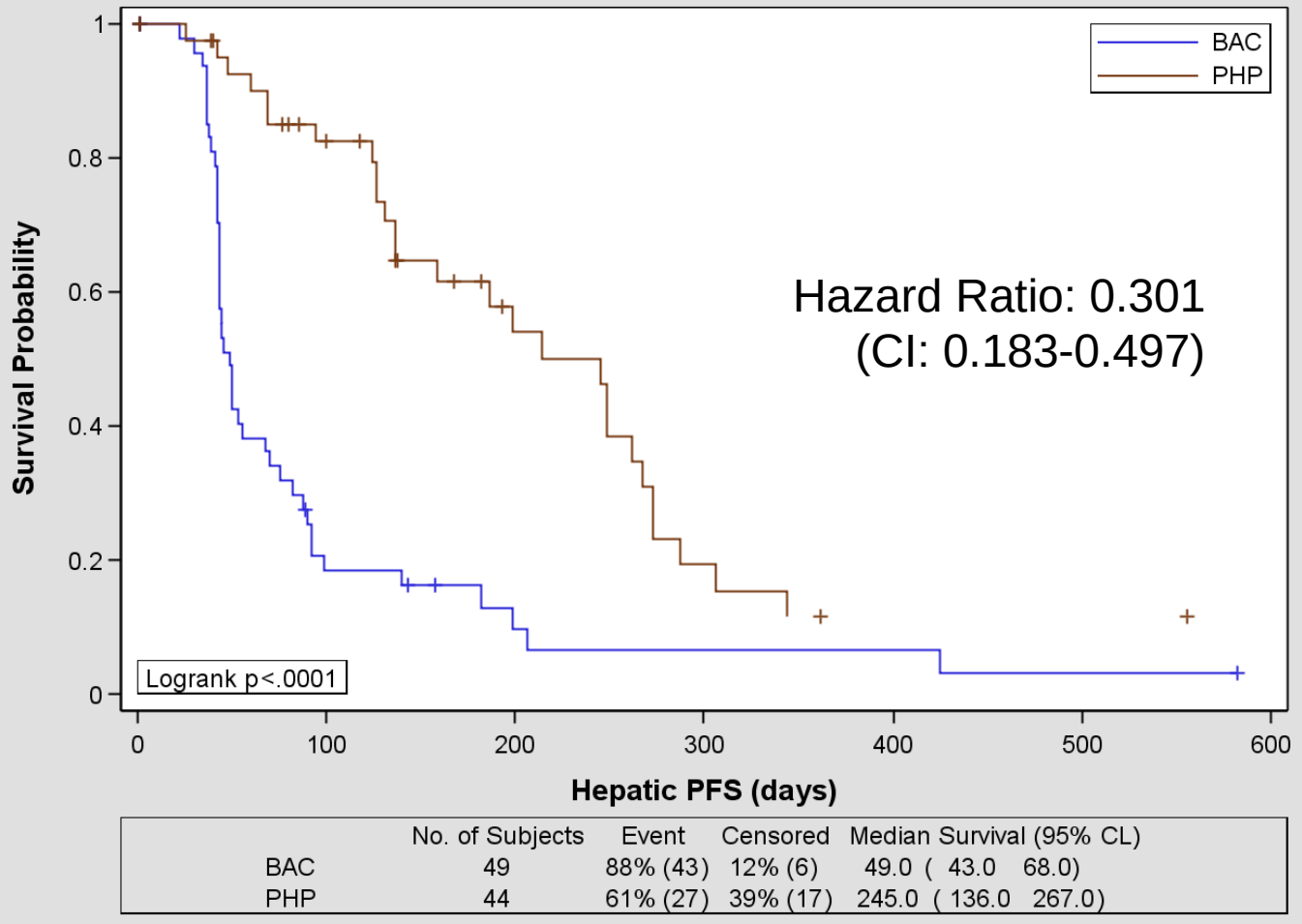
Toxicity Profile

- Most common grade 3/4 toxicities
  - Peri-procedure: thrombocytopenia, anemia and hypobilirubinemia
  - Post-procedure: myelosuppression (neutropenia)
    - Febrile neutropenia in 6 (15%) patients
- Transient peri-procedural transaminitis (10–30%)
- Non-hematological toxicities infrequent
- Three treatment-related deaths
  - Hepatic failure, n=1
  - Neutropenic sepsis, n=1
  - Pancytopenia, n=1

MRI Showing Near Complete Regression of Metastatic OM After PHP for Over 2 Years

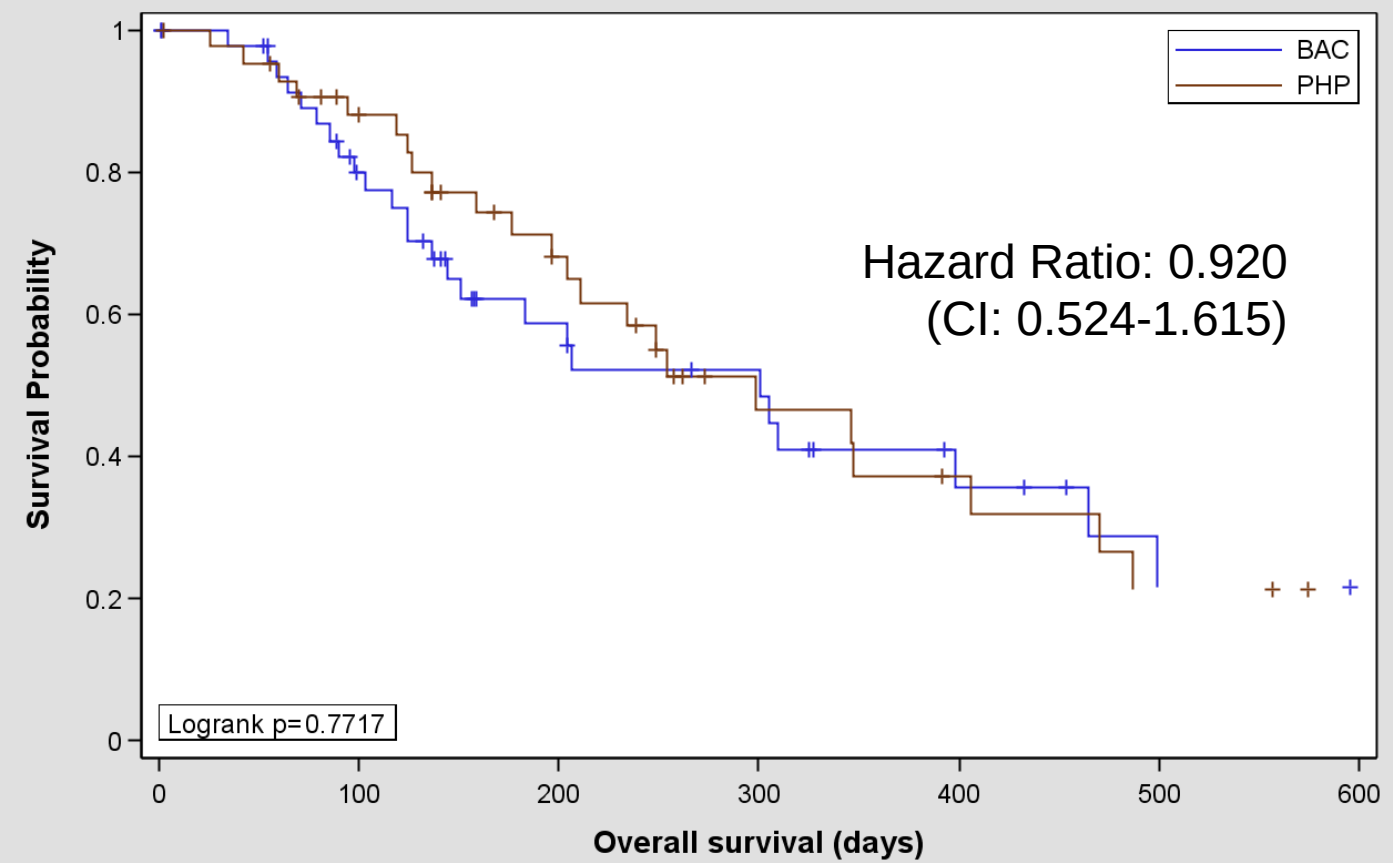


Hepatic Progression Free Survival



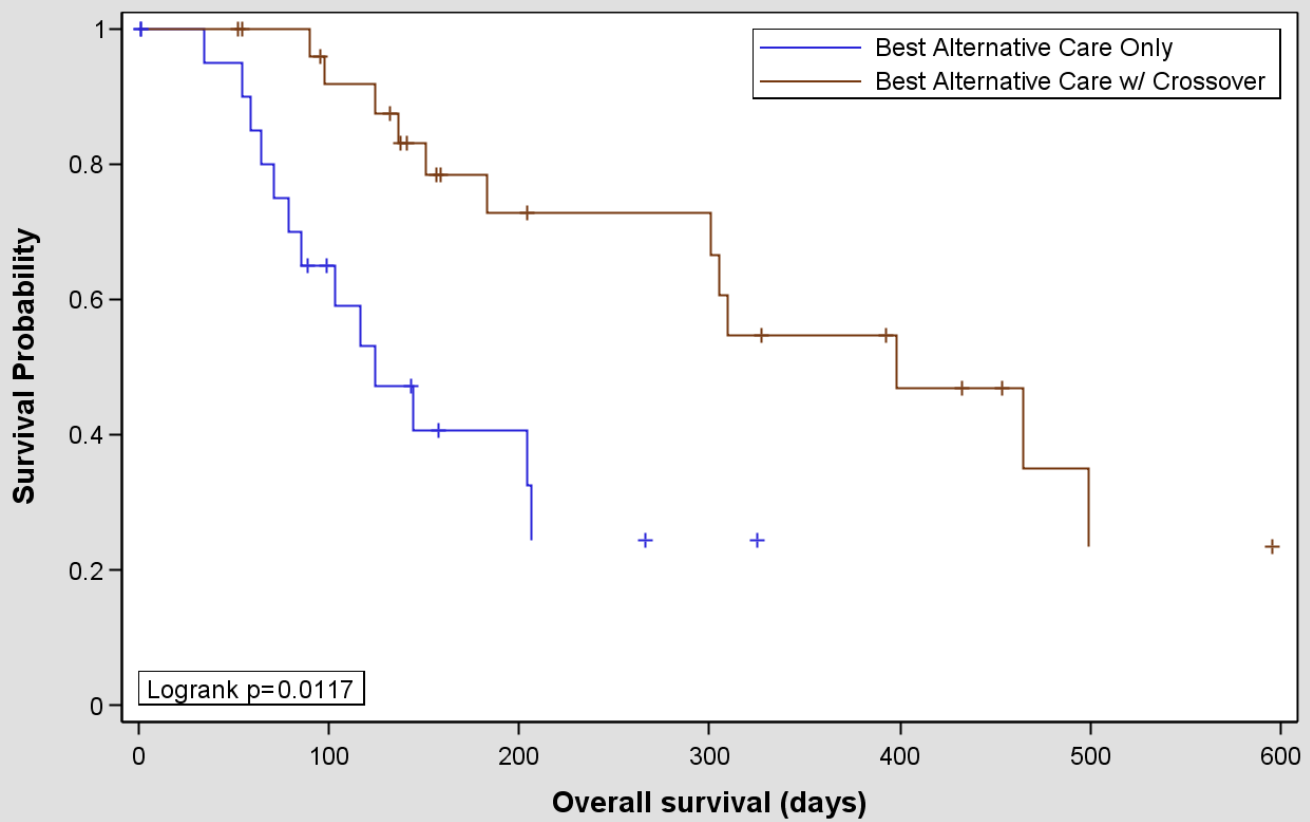
	No. of Subjects	Event	Censored	Median Survival (95% CL)
BAC	49	88% (43)	12% (6)	49.0 (43.0 68.0)
PHP	44	61% (27)	39% (17)	245.0 (136.0 267.0)

Overall Survival



	No. of Subjects	Event	Censored	Median Survival (95% CL)
BAC	49	51% (25)	49% (24)	301.0 (151.0 465.0)
PHP	44	55% (24)	45% (20)	298.0 (204.0 470.0)

Secondary Endpoint – Overall Survival BAC Patients

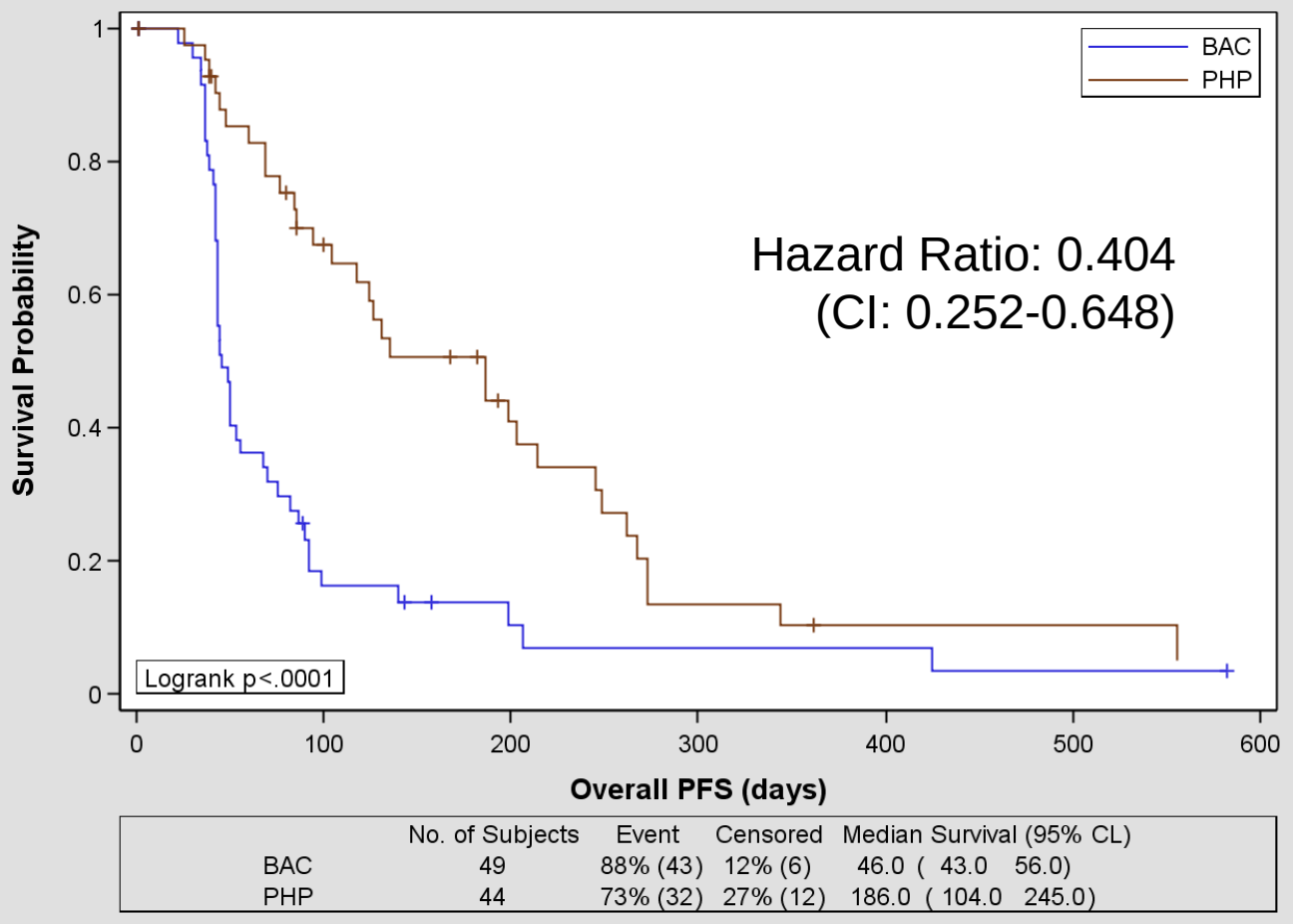


	No. of Subjects	Event	Censored	Median Survival (95% CL)
Best Alternative Care Only	22	59% (13)	41% (9)	124.0 (79.0 206.0)
Best Alternative Care w/ Crossover	27	44% (12)	56% (15)	398.0 (301.0 499.0)

Conclusions

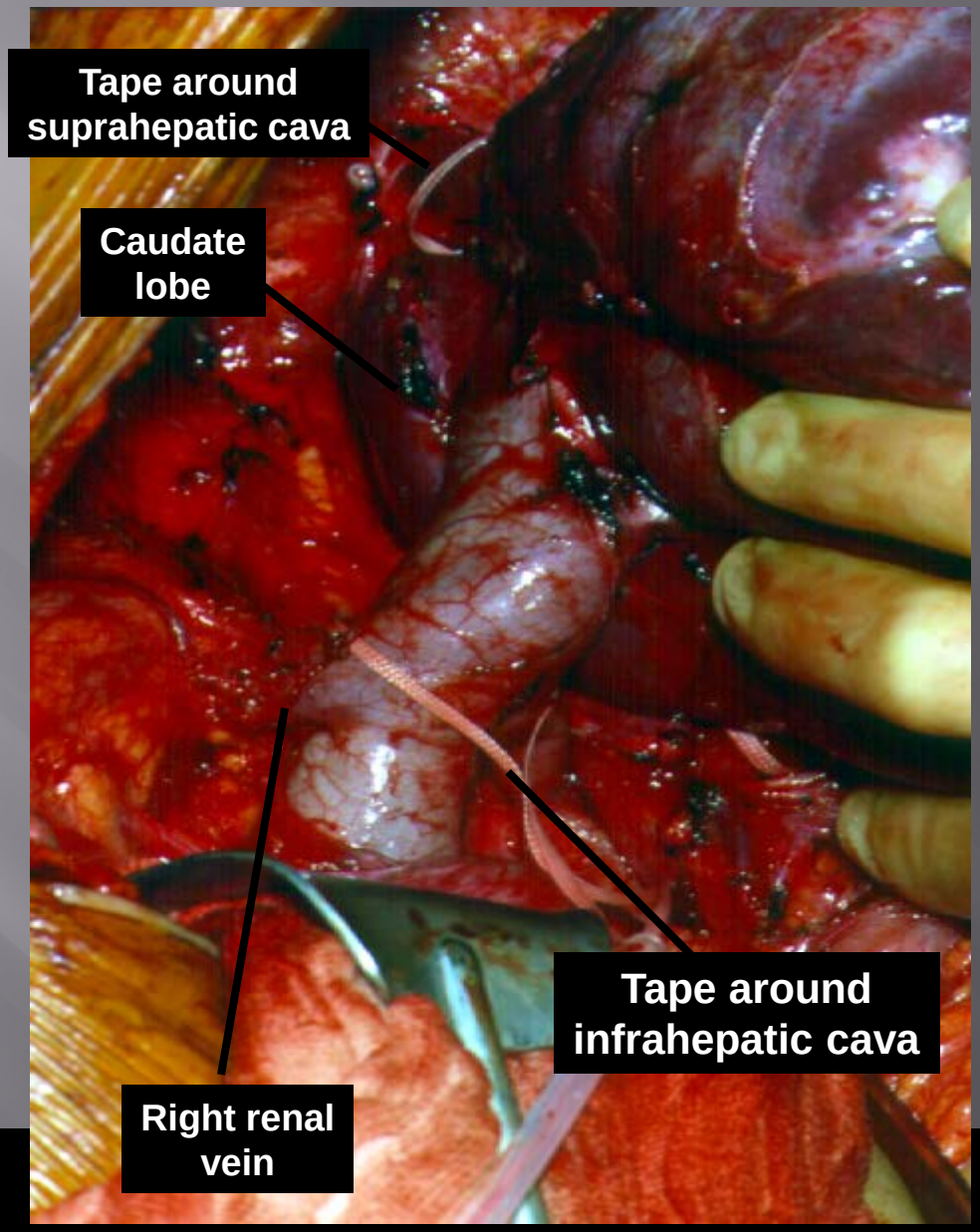
- PHP with melphalan significantly improves hPFS *vs* BAC in patients with liver-dominant metastatic melanoma
  - Primary analysis confirmed by secondary endpoints
- Overall survival not improved, ? confounded by crossover
- Crossover from BAC to PHP after hepatic disease progression was associated with prolonged survival
- PHP has activity against liver metastases from NET
- Toxicity profile manageable and as expected for melphalan
- Transient and self-limiting liver function test abnormalities

Overall Progression Free Survival (ITT)

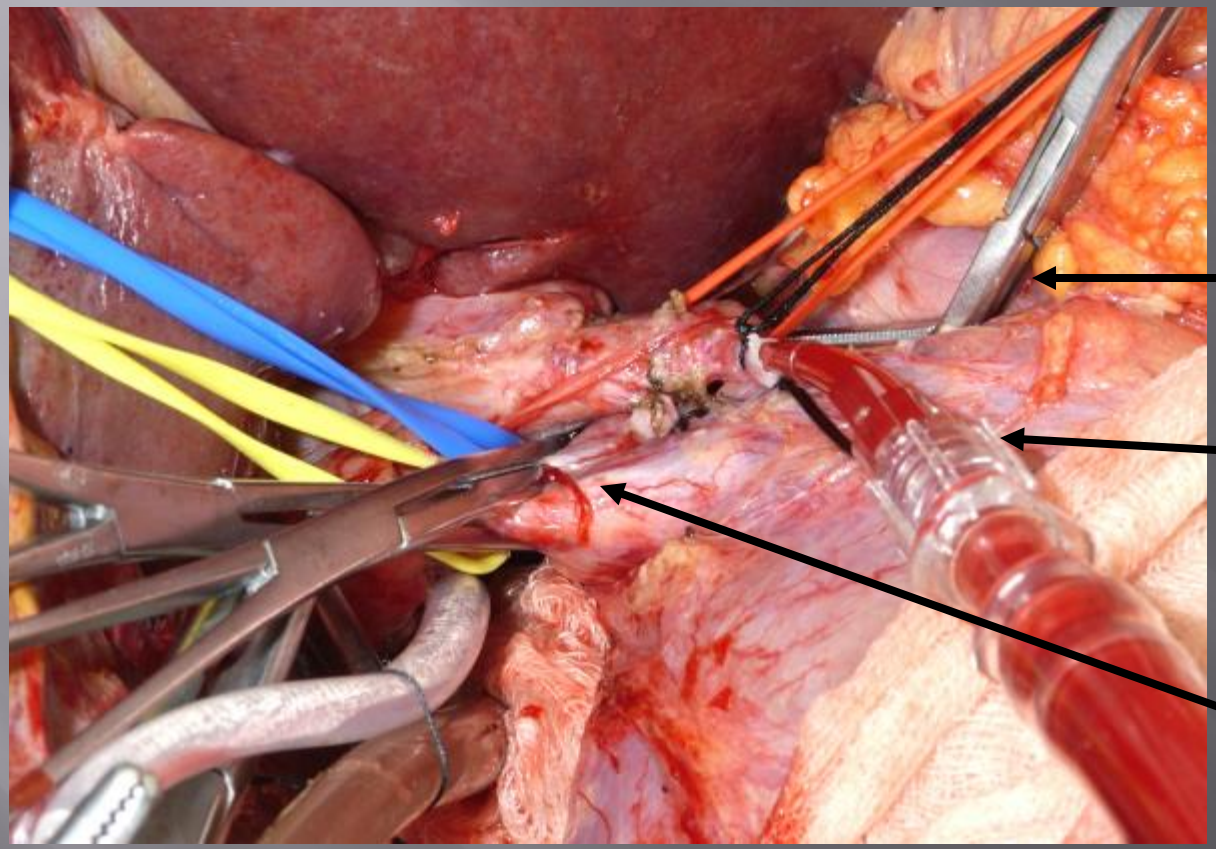


	No. of Subjects	Event	Censored	Median Survival (95% CL)
BAC	49	88% (43)	12% (6)	46.0 (43.0 56.0)
PHP	44	73% (32)	27% (12)	186.0 (104.0 245.0)

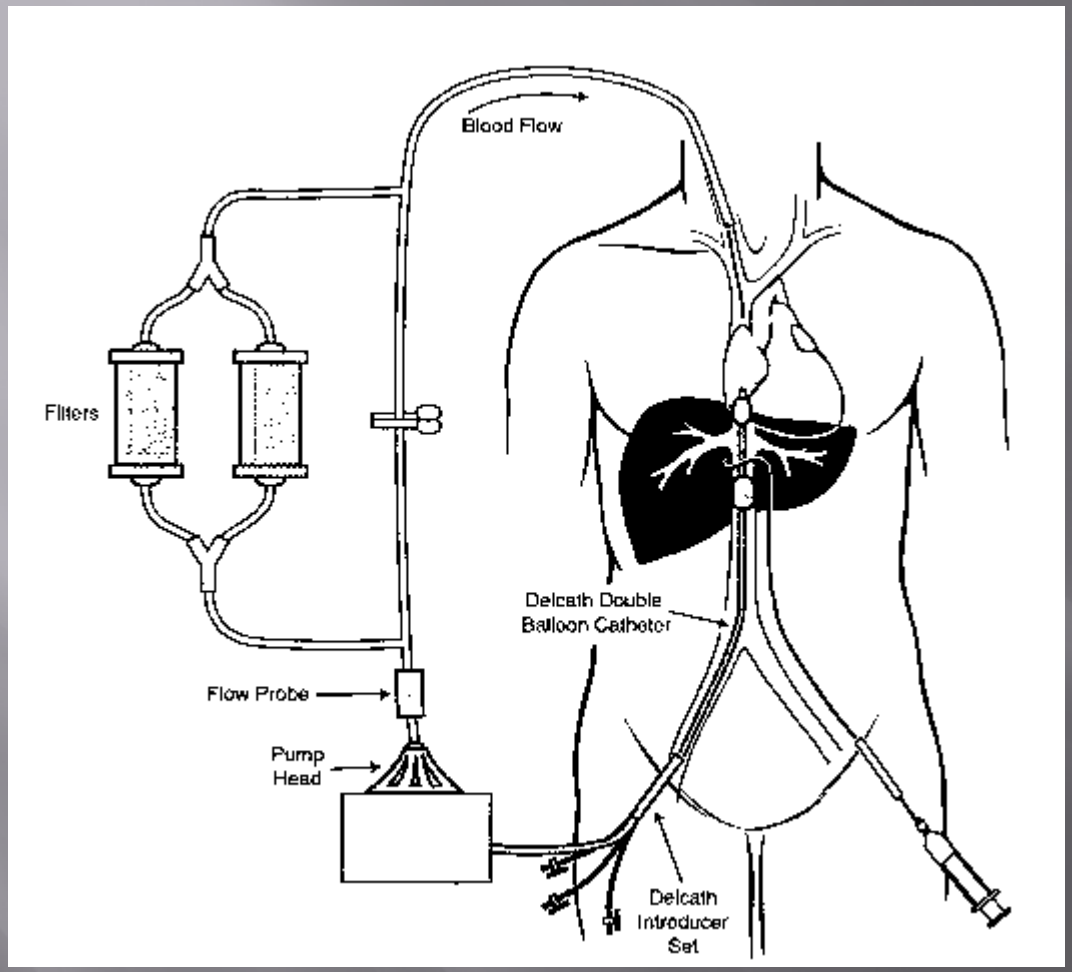
Operative View of IVC Dissection During IHP

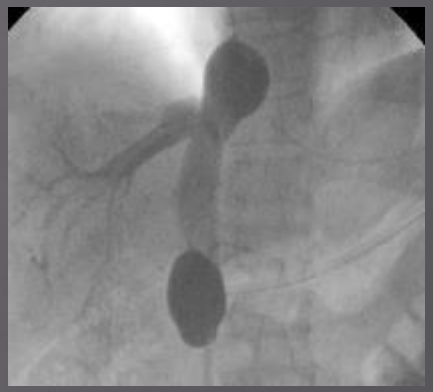


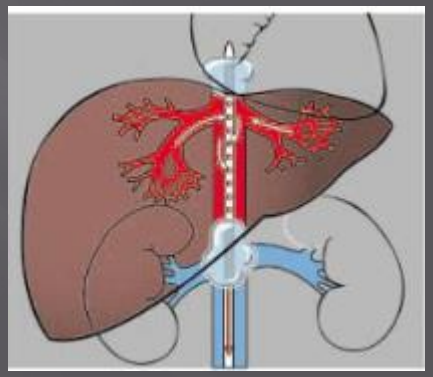
Operative View of the Porta Hepatis During IHP



Percutaneous Hepatic Perfusion







Phase II Conclusions

- PHP delivery of melphalan showed promising efficacy in patients with metastatic neuroendocrine tumors
  - Overall response rate: 58%
  - Median hepatic progression-free survival: 15.5 months
  - Median overall survival of 30 months in heavily pretreated patients
- The safety profile of PHP was manageable
- Grade 3/4 adverse events were mainly hematological
- Transient transaminitis was also observed

Melphalan: Dosage

Mode/route of administration	Melphalan dose
Multiple myeloma (oral)	0.15–0.25 mg/kg/day
Multiple myeloma (intravenous)	16 mg/m^2
Chemoembolization	0.62 mg/kg
Myeloablation (intravenous)	2.5–3.5 mg/kg
Isolated hepatic perfusion	1.5–2.0 mg/kg
Chemosaturation percutaneous hepatic perfusion	3.0 mg/kg

- Melphalan 3.0 mg/kg can be administered to the liver using PHP
- Dose deliverable by PHP is:
  - similar to that used for systemic myeloablation
  - higher than normally used with IHP (1.5–2.0 mg/kg)
  - more than 7 times higher than used for systemic therapy of multiple myeloma

Baseline Characteristics

Characteristic	No. of patients (N=23)	Percentage
Primary tumor histology		
Pancreatic neuroendocrine	17	74
Carcinoid	6	26
No. of hepatic lesions, median	15	
Mean diameter of largest lesion, cm	4.8	
Percentage of hepatic replacement		
<25%	12	52
25–50%	5	22
>50%	6	26
Extrahepatic disease	9*	39

*Subsequent resection (n=7)