

Patient Selection for Drug Eluting Bead – Irinotecan (DEBIRI): Surgical Oncologist Perspective

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www.ULBeadRegistry.com

Objectives: Considering Other Metastatic Diseases to Liver

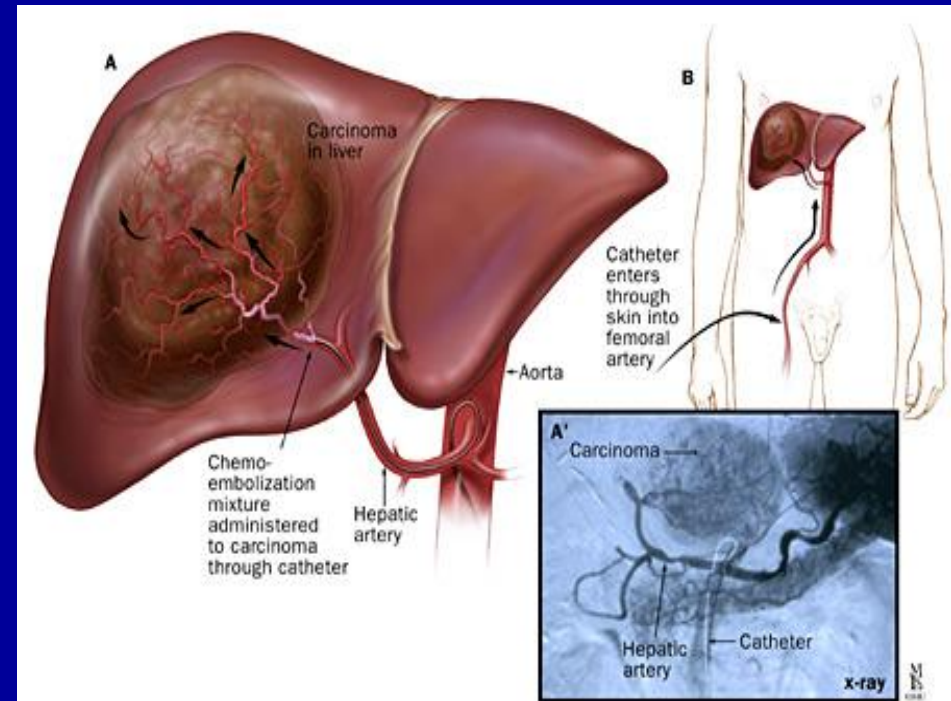
- Present the advantages of Hepatic Arterial Therapy
 - Enhanced Surgical Downstaging and Ablation
- Understand the DC Drug Eluting Bead Device in Metastatic Disease
 - Effects of Surgical Planning
- Understand the optimal use of DC Bead with Concurrent Systemic Chemotherapy
 - Optimal Collaboration with Med Onc

Is Hepatic Directed Therapy Effective in Metastatic Disease?

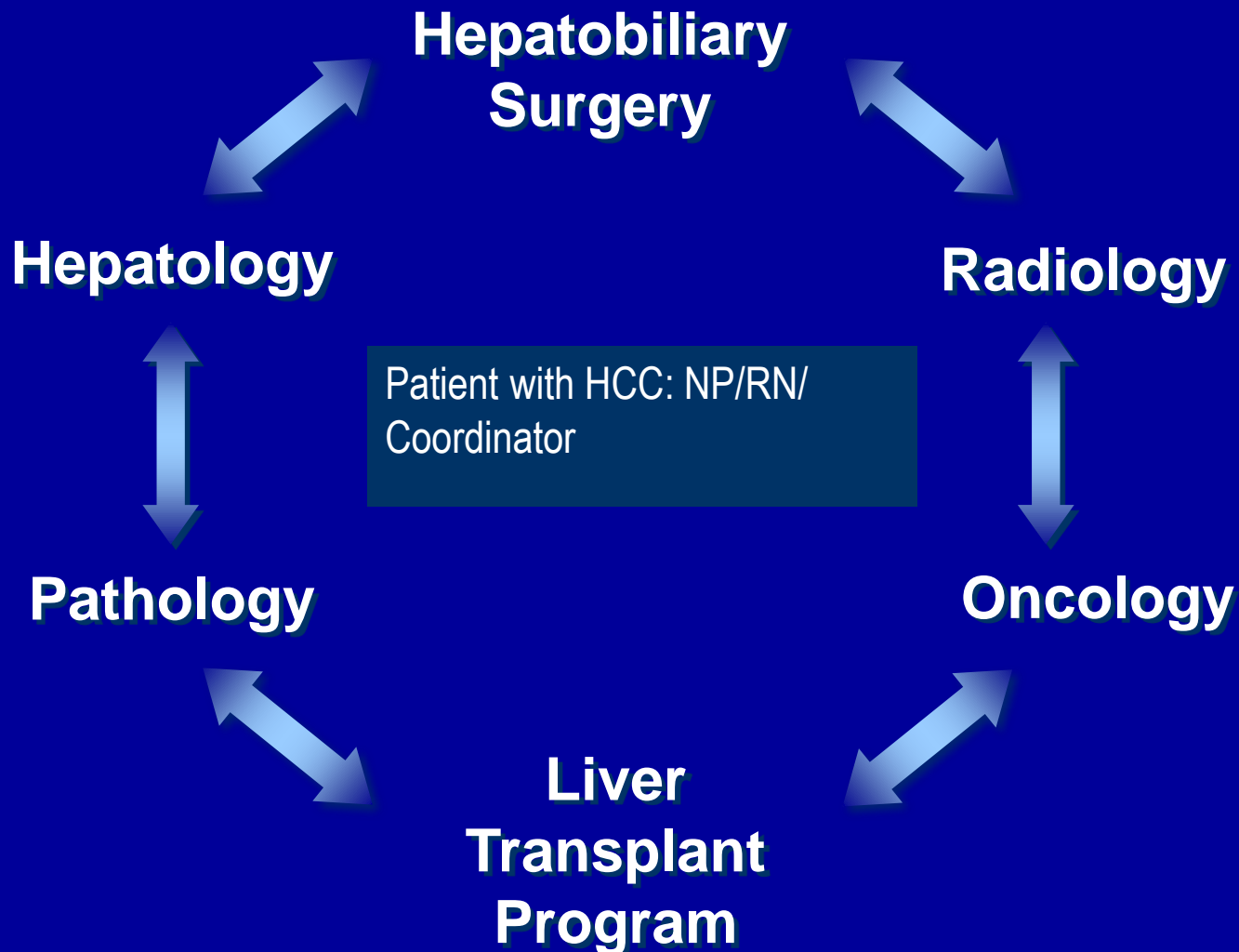
- Yes when treatment is utilized by taking in all of the patient and physician factors
 - Unfortunately no simple answer
 - Multifactorial in presentation as well as management.
 - The Main reason a multi-disciplinary team must be involved at the **initial** diagnosis.
 - Salvage therapy using: Chemotherapy, Radiation Therapy or Surgery is less optimal

Current Therapies for Metastatic Disease to Liver

- Surgical
 - Resection: Open or Laparoscopic
- Local:
 - Radiofrequency Ablation
 - Conventional Transcatheter Arterial Chemoembolization (TACE)
 - Transarterial Bland Embolization
 - **Precision Transarterial Chemoembolization**
 - Cryoablation
 - Microwave Ablation
 - Radio-Embolization
 - Hepatic Arterial Infusion
 - Irreversible Electroporation
- Systemic:
 - Chemotherapy
 - Best Supportive Care



Management of Liver Masses Requires a Multidisciplinary Approach EVERYONE WINS!



An Evolving Paradigm

THE PAST 2000



THE PRESENT 2011

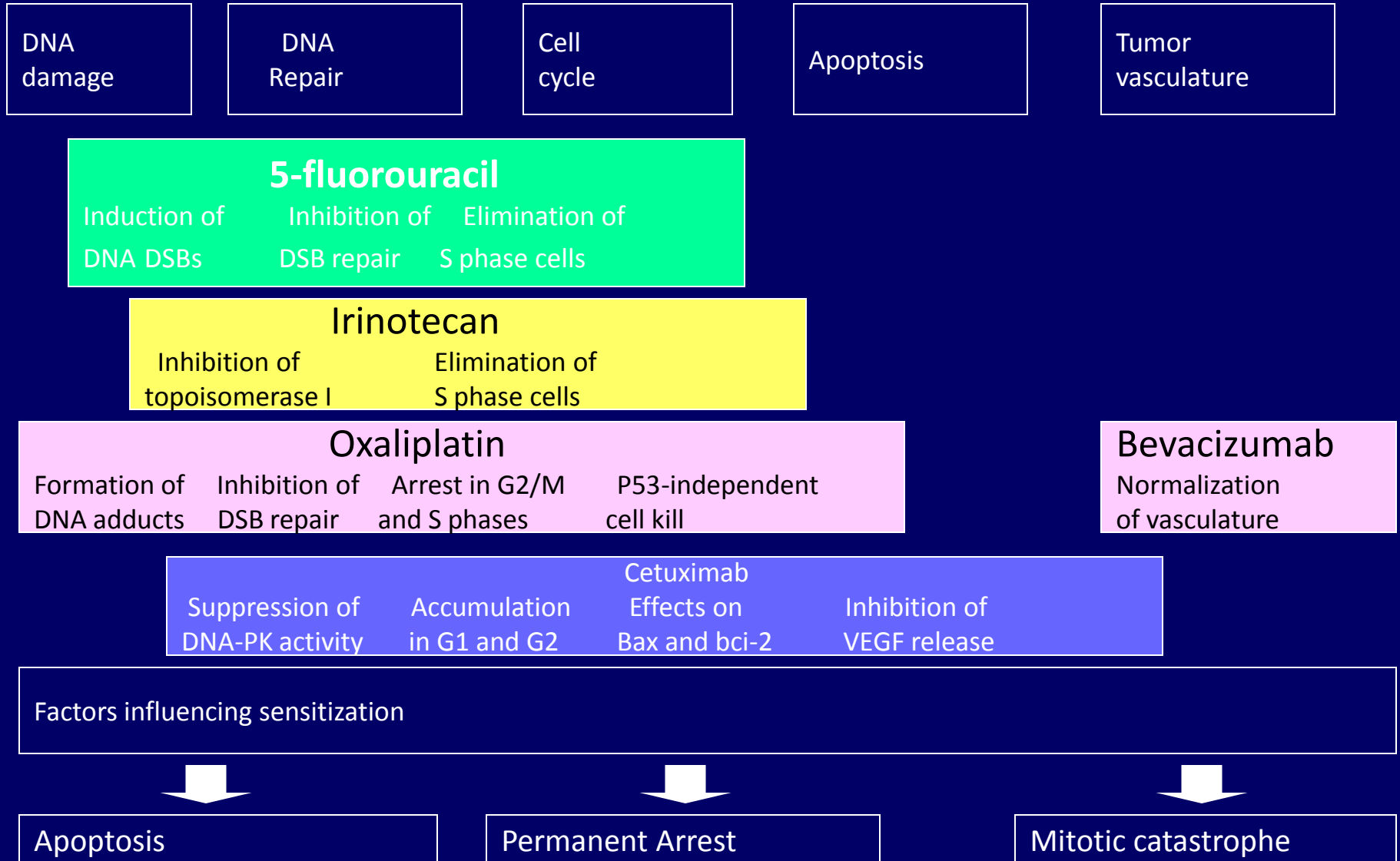


The sizes of the color-blocks are not proportionate to the numbers of patients falling into each category.

1. Adam R. Downstaging of Liver Disease for "Cure": Is this the End of Palliative Chemotherapy? ASCO 2007 Gastrointestinal Cancers Symposium. NCCN Clinical Practice Guidelines in Oncology. Colon Cancer v. 2.2007 .
2. Abdalla et al. *Ann Surg Oncol.* 2006;13(10)1271-1280.
3. NCCN Clinical Practice Guidelines in Oncology. Colon Cancer v. 2.2007.

Metastatic Colorectal Cancer

Properties of Drugs in Use for the Treatment of Metastatic Colorectal Cancer



DSB: Double Stand Break; PARP: poly-(adenosine diphosphate ribose) polymerase; DNA PK: DNA-activated protein kinase

Optimal Combinations

- FOLFOX better than FOLFIRI
 - British FOCUS study - Response rates 57% vs 49% (ns)
- FOLFOXIRI – three drug regimen
 - Greek: 150mg/m² IRI & 65mg/m² Oxal compared to FOLFIRI (ns)
 - Italian: 165mg/m² IRI & 85mg/m² Oxal
 - Higher RR 60% vs 35% and higher R0 rx
 - But with sig Grade 3/4 toxicity – 70%

Combination Chemotherapy: Optimal Response vs Toxicity

- Combination of Chemotherapeutic drugs:
 - Optimal when compared to monotherapy
- Challenges remain in combination
 - Optimal Dosing of All chemotherapeutic agents
 - Tolerance to prolonged >8 weeks therapy
- Challenges remain on the ability to deliver high enough dose to liver
 - While minimizing systemic toxicity
- Can we deliver chemotherapeutic agents in a TARGETED approach to the liver

Drug Eluting Beads

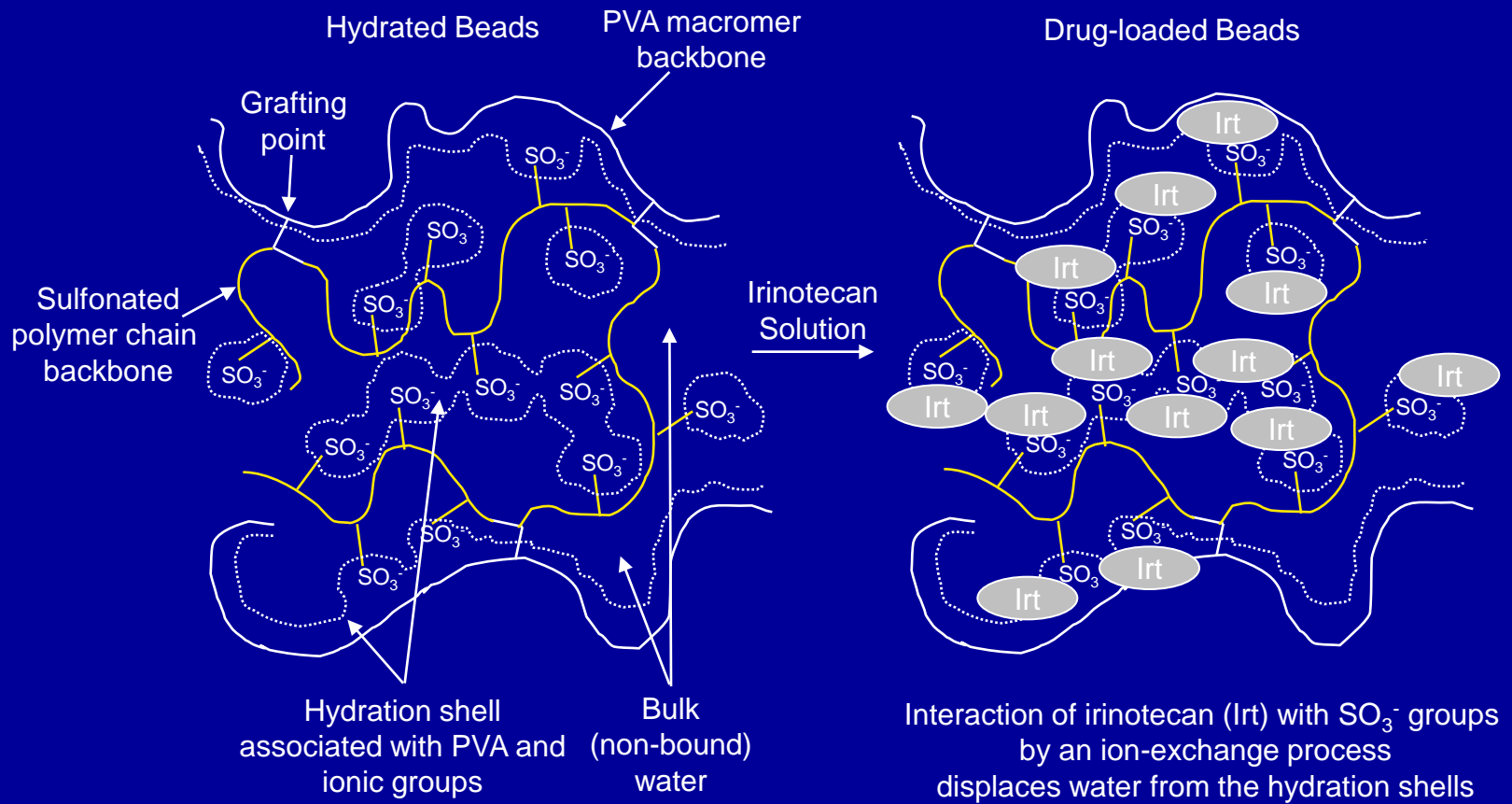
The LC Bead was designed as a drug-eluting bead that combines pharmaceutical and medical device technology to produce a device which has the potential to be more effective than either technology on its own.

Pharmaceutical compound:
Doxorubicin or **Irinotecan**

Medical Device:
Highly sulfonated, hydrogel-modified PVA embolic microsphere based on [N-fil Technology](#).



Drug Eluting Bead Loading: Charge based method



Results from International Bead Registry

Serbia	Centar Nis Serbia
Czech Republic	FH Brno FH Plzen Usti nad Labem FN v Motole Regional Hospital Novy Jicin Usti nad Orlici
Spain	Clinica Vistahermosa – Alicante Hospital Puerta de Hierro – Madrid Complejo Hospitalario de Ciudad Real Fundacion Jimenez Diaz SaluMadrid Hospital Universitario La Paz – Madrid Le Fe Hospital Hospital Arrixaca Hospital Clínico de Valencia Hospital de Alcorcón Hospital Germans Trias i Pujol Hospital Parc Taulí de Sabadell Hospital Puerta de Hierro – Madrid Hospital Universitario de Canarias Hospital Universitario de Puerto Real
Portugal	Hospital Curry Cabral – Portugal -Hospitais da Universidade de Coimbra
Russia	Center of Roentgen-Radiology, St Petersburg Regional Oncological Dispanser, Samara Oncological Center – Blochin, Moscow
USA	Baptist Health, Little Rock Huntsville Hospital, Huntsville Ala Aurora Health Care Colorado Springs North Mississippi Medical Center Mobile Infirmary Med Cen University of Louisville University of Maine U of Miami Rhode Island Hospital Covenant Health Systems Midland Memorial Rhode Island Hospital St Joseph’s
Italy	E.O. Ospedali Galliera Genoa
Germany	Diakonissenkrankenhaus Karlsruhe-Rüppur
Argentina	Hospital Italiano: Buenos Aires
Canada	University of Alberta Hospital
Brazil	Vascular Radiology and Oncology, Rio de Janeiro, Brazil

International Bead Registry

- To Date:
 - 605 patients have been treated with 1155 total Bead treatments
- Hepatocellular: 218 pts (Doxo)
- Metastatic Colorectal: 186pts (Irinotecan)
- Cholangiocarcinoma: 30pts (Irinotecan)
- Carcinoid: 48 pts (Doxo)
- Breast: 30 (Doxorubicin)
- Melanoma: 12 pts (Doxo)
- Met Lung: 12 pts (Doxo)
- Metastatic Pancreatic Cancer 4 (Irino)

Current Clinical Data – Metastatic Colorectal with DEBIRI

- Can we prove it is safe? **YES**
- Can we prove it is effective? **YES**
- Can we prove it is safe prior to surgical resection? **YES**
- Can we prove it is effective in chemorefractory patients? **YES**
- Can it be used in combination with chemotherapy?

Hepatic Intra-arterial injection of Irinotecan Eluting Beads in Unresectable Colorectal Liver Metastatic Refractory to Standard Systemic Chemotherapy: Multi- Institutional Study

**Robert Martin MD PhD, Ken Robbins MD,
Tiffany Metzger, Ryan O'Hara MD,
Petar Bosnjakovic MD, Dana Tomalty MD**

Response

Response (n=60)	3 months	6 months	12 months
Complete Response	8%	9%	12%
Partial Response	35%	22%	22%
Stable Disease	19%	30%	36%
Progression of Disease	3%	13%	18%

Compared to Best Supportive Care or Salvage: RR 2-5% at 3-6 months

Survival

Survival	Median (months)	At 1 year
PFS	11	55%
Hepatic	15	75%
Extrahepatic	13	45%
Overall Survival	19	75%

Conclusion

- Hepatic arterial infusion with Irinotecan was in the treatment of MCC refractory to multiple lines of systemic chemotherapy.
- Hepatic arterial infusion is an acceptable therapy for the treatment of metastatic colorectal cancer to the liver.

Hepatectomy Following Hepatic Arterial Therapy with Drug-Eluting Bead Chemotherapy: Is It Safe?

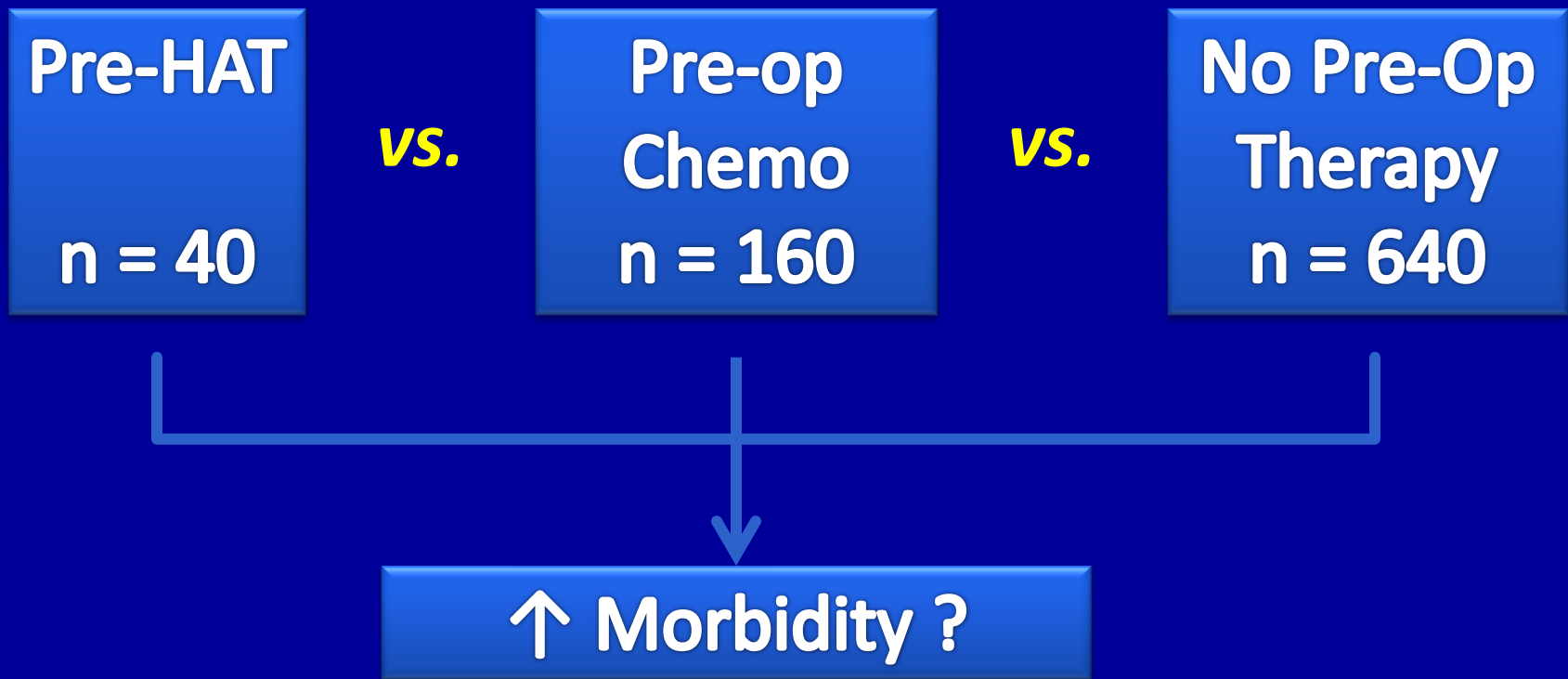
Russell E Brown, Matthew R Bower,
Charles R Scoggins, Kelly M McMasters,
Robert CG Martin II

Division of Surgical Oncology
University of Louisville
Louisville, Kentucky

Bower et al HPB 2009
Brown et al HPB 2010

Methods

- 4:1 Matched Case-Control Analysis



Group Characteristics

	Preop-HAT	Preop-Chemo	No Preop Tx	p
n	40	160	640	
Median Age (Range)	60 (27-85)	65 (35-82)	66 (25-81)	NS
Median # of Lesions	2 (1-5)	2 (1-25)	1 (1-7)	NS
Max Lesion Diameter	3.5 cm (1.5-9.5)	4 (1.2-9)	4 (1.5-8)	NS

Pre-HAT Therapies (n=40)

- Total Treatments 92
- Yttrium-90
 - Total Treatments 18
 - Median Treatment per pt 2 (1-2)
- DEB-Irinotecan
 - Total Treatments 37
 - Median Treatment per pt 2 (1-6)
- DEB-Doxorubicin
 - Total Treatments 37
 - Median Treatment per pt 2 (1-6)

Chemotherapy History

- Both the pre-HAT and pre-op Chemo Groups had chemotherapy exposure

	Pre-HAT n = 40 pts	Pre-op Chemo n = 160 pts
FOLFOX	7	105
FOLFIRI	7	31
Sorafenib	3	0
Gemcitabine	3	4
Bevacizumab	7	55
5-FU	6	32
Other	18	16

Pathologic response

- No chemotherapy associated sinusoidal obstruction.
- Minimal fibrosis.
- Overall pathologic response 30-90% necrosis.

Peri-Operative Data

	Pre-HAT N=40	Pre-op Chemo N=160	No Pre-op Tx N=640	p
Right Hepatectomy	18 (45%)	90 (56%)	281 (44%)	0.30
Median EBL (mL)	550	400	375	0.42
Need for Transfusion during Hospital Stay	10 (25%)	77 (48%)*	192(30%)	0.04

Endpoints

	Pre-HAT N=40	Pre-op Chemo N=160	No Pre-op Tx N=640	p
Complication, Any Grade	13 (32%)	56 (35%)	147(23%)	.7
Complications, Grade ≥3	6 (15%)	22 (14%)	76(12%)	.08
Liver Specific Complications	2 (5%)	12 (8%)	44(7%)	0.2
90-day Mortality	0	6 (4%)	32 (5%)	0.7

Conclusions

- Hepatectomy after HAT demonstrates similar overall and liver-specific morbidity to resections with or without preoperative chemotherapy.
- Pre-HAT is safe and should not preclude hepatectomy in well-selected patients.

**Combination FOLFOXDEBIRI
Trial:
Concomitant Systemic
Fluorouracil, Oxaliplatin
chemotherapy, and Avastin
Therapy with concurrent DEBIRI**

Inclusion:

- Patients over 18 years of age,
- **Patients with liver dominant disease defined as $\geq 80\%$ tumor body burden confined to the liver**
- Patient has no previous treatment with chemotherapy for their stage IV colon cancer
- **Less than 60% liver tumor replacement**
- **Defined as surgically unresectable by HPB surgeon**

Feasibility Study: n=10 Patients

- **Concurrent full dose: mFOLFOX6 +/- Avastin**
 - Oxaliplatin 85mg/m²
 - with 2 LC Bead™ treatments (100mg irinotecan)

- **Schema:**

Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7
FOLFOX + Avastin	LC Bead 100mg Irino	FOLFOX +Avasti n	LC Bead 100mg Irino	FOLFOX + Avastin	Break	FOLFOX + Avastin

Then repeat CT to evaluate initial response

FOLFOXDEBIRI: Baseline: 10 Pts

	63 (48-84)
Gender (M/F)	6/4
Race (AA/C)	3/7
Prior Cancer Therapy	
Lymphoma	1
Endometrial	1
Prior Liver Surgery	RFA = 2
Laboratory Parameters	
T bili	0.4 (0.3-0.6)
Creat	0.9 (0.7-1.5)
CEA (median, range)	386 (2.6 -2893)
ECOG Performance Status	
0	5
1	5
Colon/ Rectum Primary (In place)	
Colon	7 (2)
Rectum	3 (3)
Presence of Extra-Hepatic Disease (Yes/No)	5/5 (Lung/Peritoneum)
Extent of Overall Tumor Burden in Liver	100% = 5, 95% = 2, 80% = 3

LC Bead Treatments: (n=28)

Number of Bead courses 1 & 2 DEBIRI 1, 2, & 3 DEBIRI 1,2,3, & 4 DEBIRI	5 pts 2 pts 3 pts
Treatment Location Right Left	16 12
Level of Branching Lobar	100%
Bead Size 100-300 Degree of Occlusion Technical Success Dose Delivered	100% None – 100% 100% 100mg
Length of Stay	23 hours (23 hr to 2 days)

FOLFOXDEBIRI: Extent Liver

Total # Liver Lesions (median, range)	4 (3-25)
Liver Involvement (median, range) %	35% (25-50%)
Total Target Lesion(s) Size (median, range)	11.5 (6.4 – 22.1)
Non Target Lesion	Yes = 4
Chemotherapy (All Full dose)	
FOLFOX	4
FOLFOX + Avastin	6

No Dose Limiting Toxicity and No Dose Reductions in systemic chemotherapy

Radiologic Response

Hepatic RR:

3-month: 100% (2 CR,8 PR)

6-month RR: 100%

9-month RR: 100%

12-month RR 100%

Overall RR:

3-month 100%

6-month 80%

9-month 60%

12-month 50%

	9 mon	12 mon	18mon	24 mon
CR	CR	CR	CR	RX
CR	CR	CR	CR	CR
POD Lung	CR:liver AWD	DOD		
POD: lung	DOD			
RX	CR: Liver POD: lung	CR:Liver	CR:Liver	CR:Liver
CR	CR	CR	CR	CR
CR	CR:Liver POD: Perito			
CR:Liver SD:Lung	CR:Liver SD:Lung			
10	CR	CR	CR	CR

Surgical Downstaging

- **4 (40%) patients downstaged to resection**
- **All tolerated surgical resection**
- **Pathologic response rates >90%**

FOLFOXDEBIRI GM PT #5

- 56 AA, PMHx 3 drug HTN
- Thyroid Cancer 19 y/o
- Presented with synchronous right colon and liver metastasis
- Undergoes right hemicolectomy
- Unresectable – Bilobar Disease and <20% FLR

FOLFOXDEBIRI GM PT #5

- 4 cycles of FOLFOX and Avastin
- 2 doses LC Bead – 100m Irinotecan
- SAE's – Uncontrolled HTN on day 1, 2nd bead treatment, one extra day hospital
- No dose limiting toxicity
- Follow Up October 16th

Response Rates

- After 4 cycles and 2 DEBIRI treatments
- After additional 4 (total 8) & 1 DEBIRI
- After all 12 cycles FOLFOX+Avastin and 3 DEBIRI
- Right Portal Vein Embolization
- Extended Right Hepatectomy
- No Complications with a 6 day LOS
 - Peak T bili 2.6 day 2

Pathology Response Rates

- 8 tumors (Size 0.8cm – 3.5cm) Margin -
- Non-neoplastic liver mild-moderate inflammation
- Tumor with >95% tumor necrosis

Phase 1: Summary

- Four (40%) patients were successfully downstaged to resection and/or ablation with a median overall survival of 15.2 months
- **Conclusion:** Concomitant DEBIRI and FOLFOX +/- bevacizumab is safe, with a minimal adverse event rate, no dose-limiting toxicities, and enhanced overall response rate.

Design: First Line Metastatic Colorectal Cancer

Randomize: N=60

1 : 1

Arm A (standard)

Chemotherapy:

- 1) Bevacizumab 5 mg/kg on d1 if indicated based on last surgical date
- 2) FOLFOX regimen (oxaliplatin 85 mg/sqm d1, l-LV 200 mg/sqm d1 and 5FU 3200 mg/sqm 48- flat continuous infusion starting on d1) repeated every 2 weeks

Arm B (experimental)

Chemotherapy:

- 1) Bevacizumab 5 mg/kg on d1 if indicated based on last surgical date
- 2) FOLFOX regimen (oxaliplatin 85 mg/sqm d1, l-LV 200 mg/sqm d1 and 5FU 3200 mg/sqm 48- flat continuous infusion starting on d1) repeated every 2 weeks

i.a. Irinotecan DEB:

Irinotecan 2 ml DEB – 100mg at week 1 and week 3
2-6 cycles
at investigator's discretion based on response, toxicity, tumour burden.

Phase 2: Participating Centers

Principal Investigator	Approved	Pts enrolled
Dr Robert Martin :University of Louisville	8/31/2010	9
Dr Marshall Schreeder Clearview Cancer	12/14/2010	3
Dr John Kauh : Emory Healthcare	8/28/2010	1
Dr William Rilling :Froedtert Hospital	10/27/2010	1
Dr Nishan Fernando : Northside Hospital	9/28/2010	0
Dr Michael Rush : Holy Cross Hospital	10/28/2010	0
Dr Chris Laing : Radiological Associates	4/14/2011	1
Dr Todd Crocenzi ; Providence, Port, OR	2/15:2011	1
Dr. Ricardo Garcia Monaco : Hospital Italiano	5/12/2011	0
Dr. Steven Strasberg : Wash University	4/2/2011	3
Dr. Jim Papalouis : INOVA Healthcare	5/19/2011	0
Dr Jose Hugo Mendes Luz : INCA – Rio, Br.	Pending	Opening

COLO-RECTAL CANCER: THE PAST

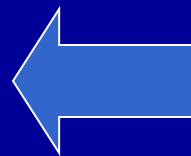
LIVER METASTASES

Resectable 10-20%

Non resectable 80-90%



Increasing
Resectability



Optimizing
Chemotherapy

EVOLUTION OF RESECTABILITY

~~1- Age-related~~

~~2- Tumor-related~~ : related to hepatic
metastases



- Number of tumors



- Tumor Size...

~~3- Disease-related~~ : curative pattern of resect



Resection Margin



Extrahepatic site

~~4- Technical~~ : Too small remnant liver

(< 30% total functional liver)

COLO-RECTAL CANCER

LIVER METASTASES

Expanding indications

Resectable 20-30%

Non resectable 70-80%

Surgery

20-40%

**Optimizing
Chemotherapy/
Delivery**

Intra-Hepatic Cholangiocarcinoma

Precision Hepatic Arterial Irinotecan Therapy in the Treatment of Unresectable Intrahepatic Cholangiocarcinoma: Optimal Tolerance and Prolonged Overall Survival

Suzanne C Schiffman MD¹, Tiffany Metzger, BS¹,
Gregory Dubel, MD², Tomas Andrasina, MD³,
Ivan Kralj, MD⁴, Cliff Tatum, MD⁵, Kelly M
McMasters MD PhD¹, Charles R Scoggins MD
MBA¹, and Robert CG Martin MD PhD¹

1: Division of Surgical Oncology, Department of Surgery, University of Louisville, and the James Graham Brown Cancer Center, Louisville, KY and the Division of Surgical Oncology, Department of Surgery.

2: Department of Interventional Radiology, Rhode Island Hospital

3: Department of Radiology, FN Brno a LF MU Brno, Czech republic

4: Klinik für Radiologie, Interventionsradiologie und Nuklearmedizin
Diakonissenkrankenhaus

5: Norton Radiology, Norton Healthcare, Louisville, Ky.

Pre DEB (N=25 patients)

Age, median (range)	59 (XX-XX)
Gender (M,F)	9,16
Prior Hepatectomy	7pts
Prior RFA	3pts
Prior Chemotherapy	
Gemzar	7 pts
Ox +/- Avastin	4 pts
FOLFOX	1 pts
Other	2 pts
BMI (kg/m ²)	25.52

Total # of Lesions	3 (1-25)
% Liver Involvement	
<25%	8
26-50%	11
>50%	4
Target Lesion Size	11.5cm (4-33.3)
Extra-hepatic Dz	10 Patients
Lymph Nodes	5
Bone	2
Peritoneum	1
Lung	1
Mouth	1

DC/LC Bead Treatments

- Total 42 treatments
 - 1 treatment (26 pts)
 - 2 treatment(12 pts)
 - 3 treatment (4 pts)
- Irinotecan
 - 35 treatments (83.3%)
 - 75 mg
- Doxorubicin
 - 7 treatments (16.7%)
 - 150 mg

Hepatic Artery Location	
Right	51%
Left	43%
Middle	5%
Bead Size (micron)	
100-300	71%
300-500	17%
500-700	2%
100-300 then 300-500	10%
Degree of Occlusion	
Complete	46%
Near	33%
Partial	21%
Technical Success	100%

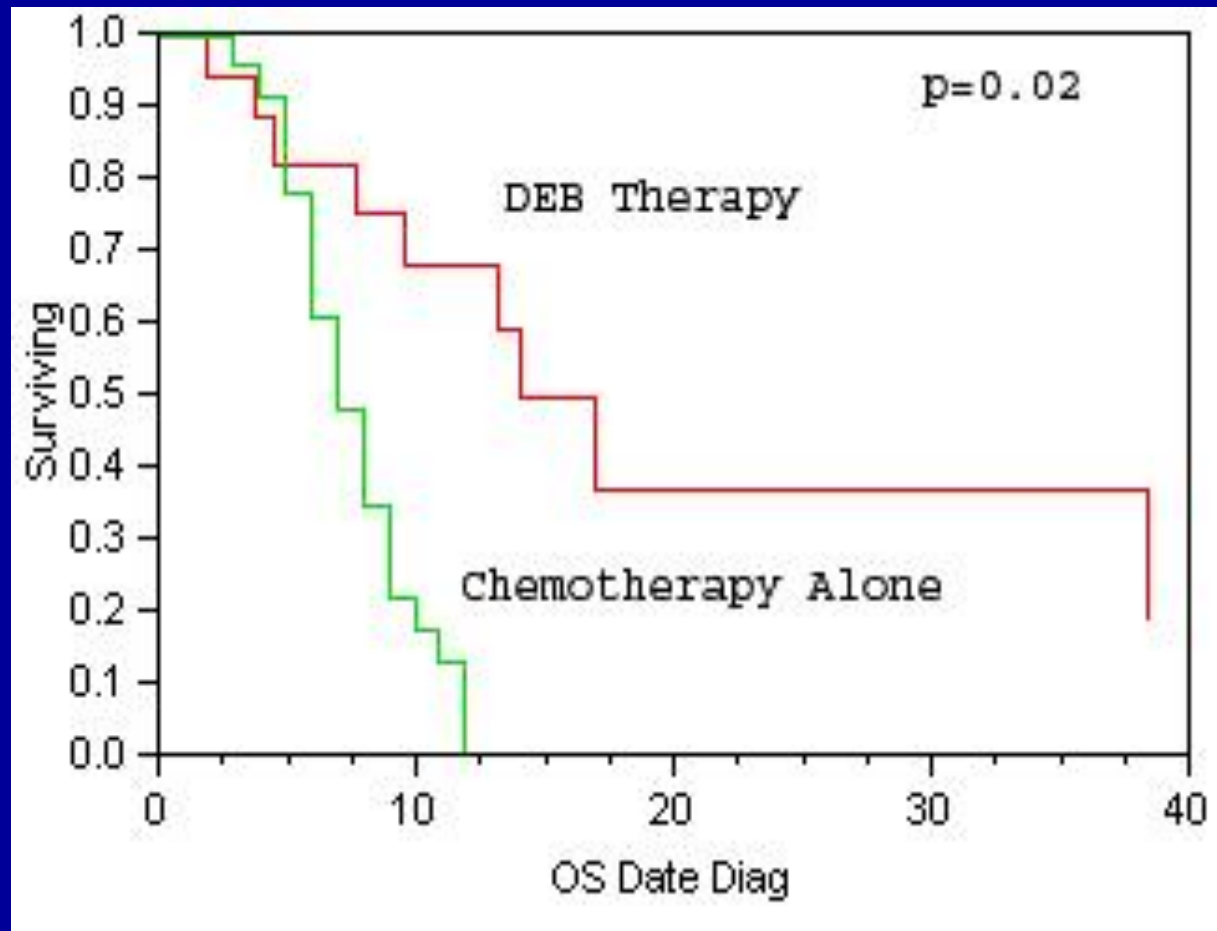
Adverse Events

- 11 (26.2%) adverse events
 - 7 (63.6%) minor
 - 4 (36.3%) major
- Mortality
 - 11 cm lesion in segment 5
 - 51-75% liver involvement.
 - One DEBIRI treatment (100 mg)
 - No prior interventions
 - DOD at 12 days
- Definition: Post-embolization syndrome (nausea, emesis, fevers and abdominal discomfort)

Complication	Grade	#AE
Post-embolization syndrome	1 to 2	4
Pneumonia	2	1
Atrial fibrillation	2	2
Hepatic Insufficiency	3	2
Sepsis	4	1
Hepatorenal Death	5	1

OVERALL SURVIVAL

- Multi-therapy with DEB
 - 17.5 months
- Best Chemotherapy
 - 9.3 months
- $p=0.02$



CONCLUSIONS

- DEB was safe and effective in the treatment of unresectable ICC
- Exhibited significantly longer overall survival time as compared to patients treated with chemotherapy only.
- Results of this study confirm the need for randomized prospective trial

CLINICAL TRIAL

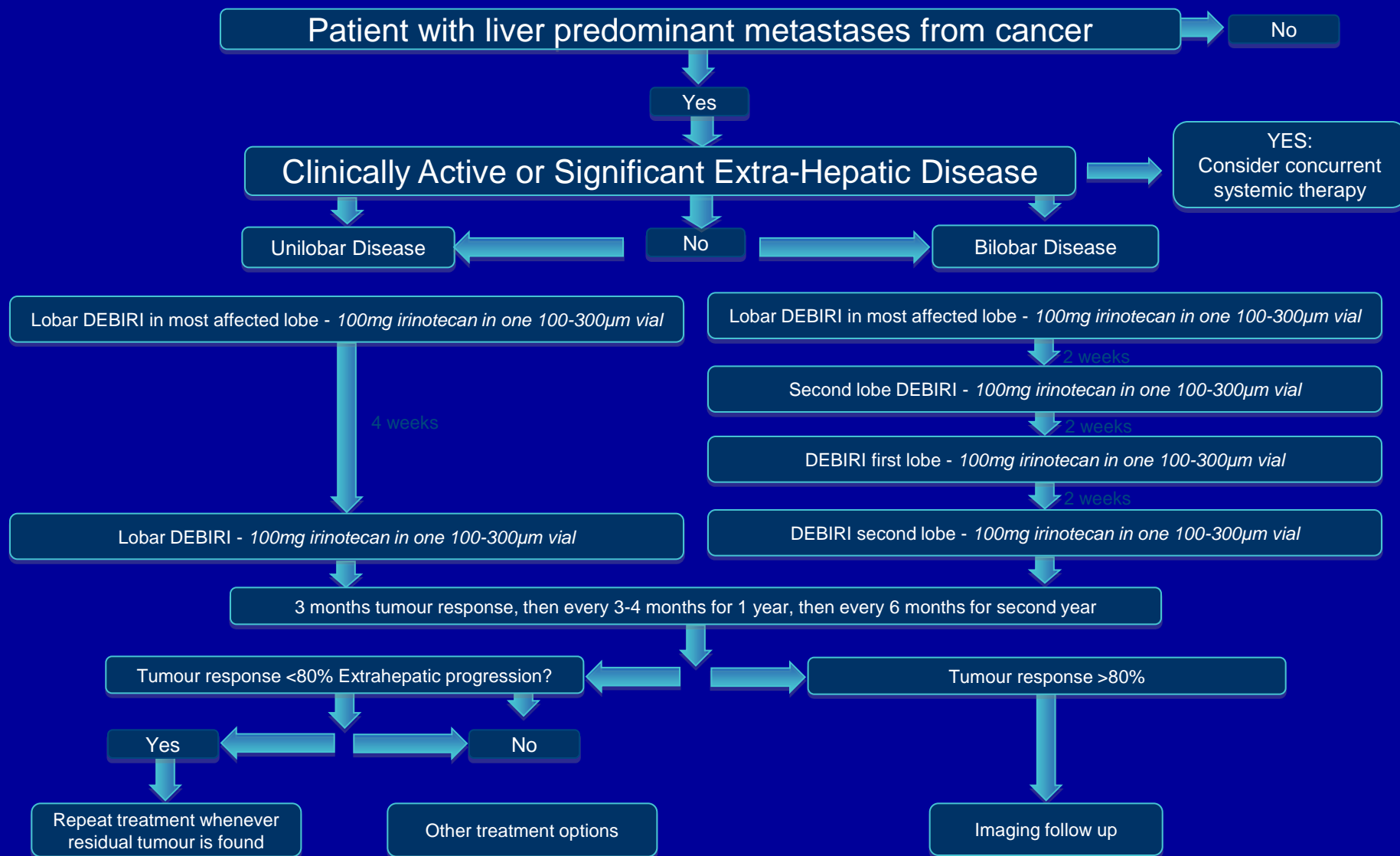
Unresectable
ICC
Randomized

- Multicenter, prospective randomized clinical trial
- Compare systemic Gemcitabine/Cisplatin to systemic Cisplatin
- Endpoints
 - Time to progression
 - Progression free survival
 - Hepatic progression free survival
 - Overall survival
- Commence May 2010 – Look for collaborative institutions

Gem/ Cist

Gem/Cis with
DEBIRI

DEBIRI Bead ALGORITHM — Liver Dominant Metastases



□Note: These notes are for guidance only and should not be seen as a recommendation or used in isolation to make clinical decisions that relate to patient care or medication.

Summary

- DC Bead with Irinotecan (DEBIRI) is safe and effective in metastatic disease to the liver
- Keys are:
 - Defining patients who have liver dominant dz
 - Collaboration with medical oncologist
 - Appropriate treatment strategy and follow up

Thank you