IS THERE A ROLE FOR INTRA-ARTERIAL THERAPY OR ISOLATED LIVER PERFUSION?

Pr Olivier Detry

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IS THERE A ROLE FOR INTRA-ARTERIAL THERAPY OR ISOLATED LIVER PERFUSION?

YES!

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Disclosure statement

- No financial relationships to disclose !

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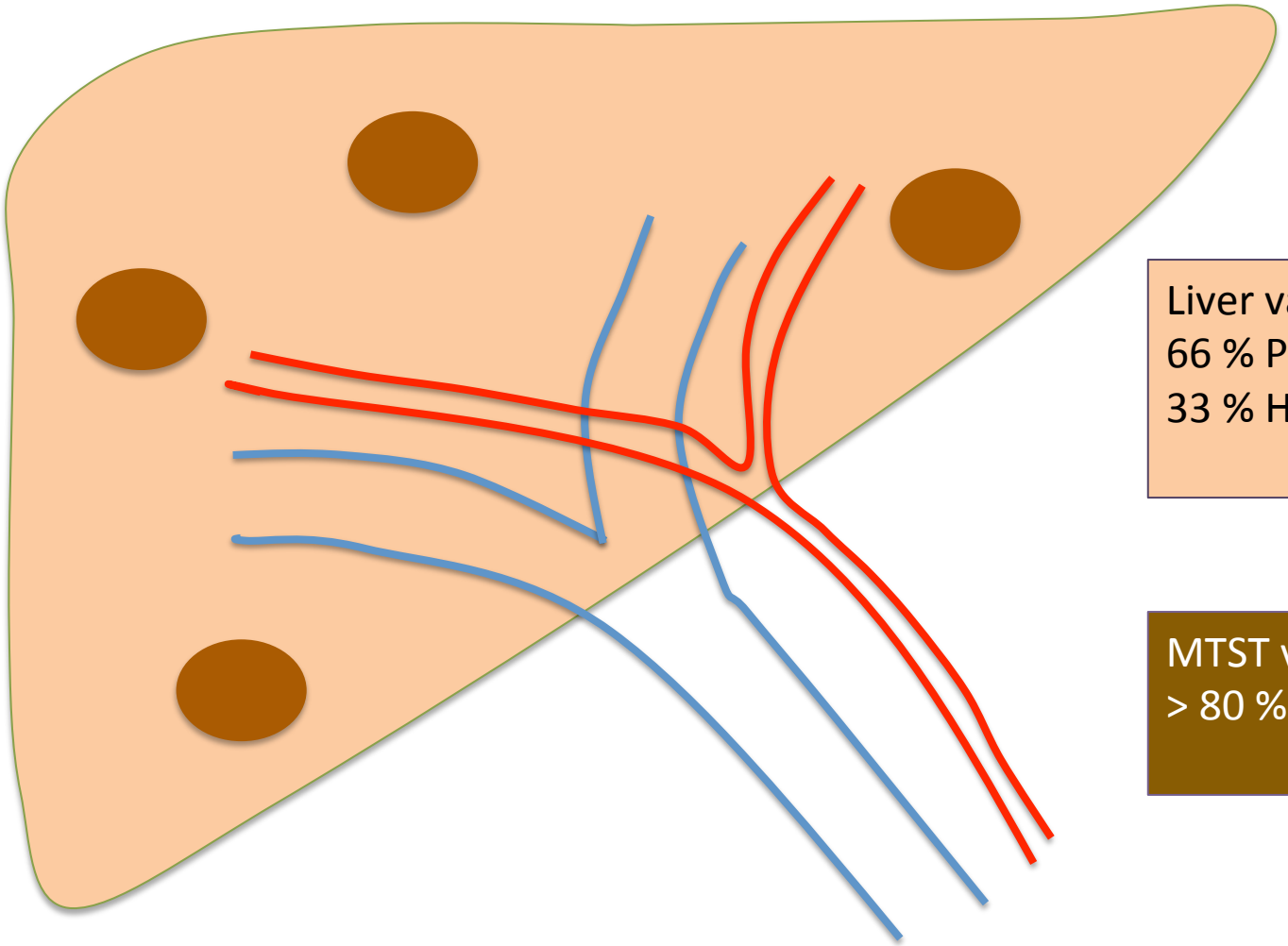
CRC Liver Mets

- 25% of patients with CRC have synchronous liver Mets at time of diagnosis
- 50% of patients will develop metachronous Mets
- R0 resection remains the standard of treatment and the only hope for cure and long-term survival
- Survival after resection: 25 to 50% at 5 years
- 50% of recurrences within 2 years
- 25 to 50% of recurrences are intrahepatic only

CRC Liver Mets



Liver vascularisation:
66 % Portal vein
33 % Hepatic artery

MTST vascularisation:
> 80 % Hepatic artery

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CRC Liver Mets
and intraarterial therapy

- Intra arterial chemotherapy
- Radioembolisation Yttrium

- Isolated liver perfusion

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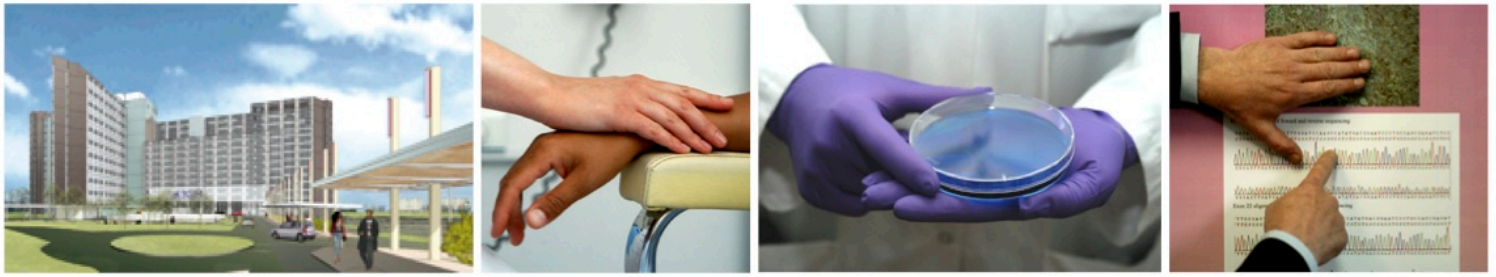
Intra-arterial chemotherapy

- Adjuvant IA chemotherapy
- Irresectable MTST
  - palliative (1st or 2nd line)

- Better compared to old style chemotherapy
- Discussed compared to modern iv therapy



Intérêt d'une chimiothérapie intra-artérielle adjuvante chez les patients à risque élevé de récidive hépatique

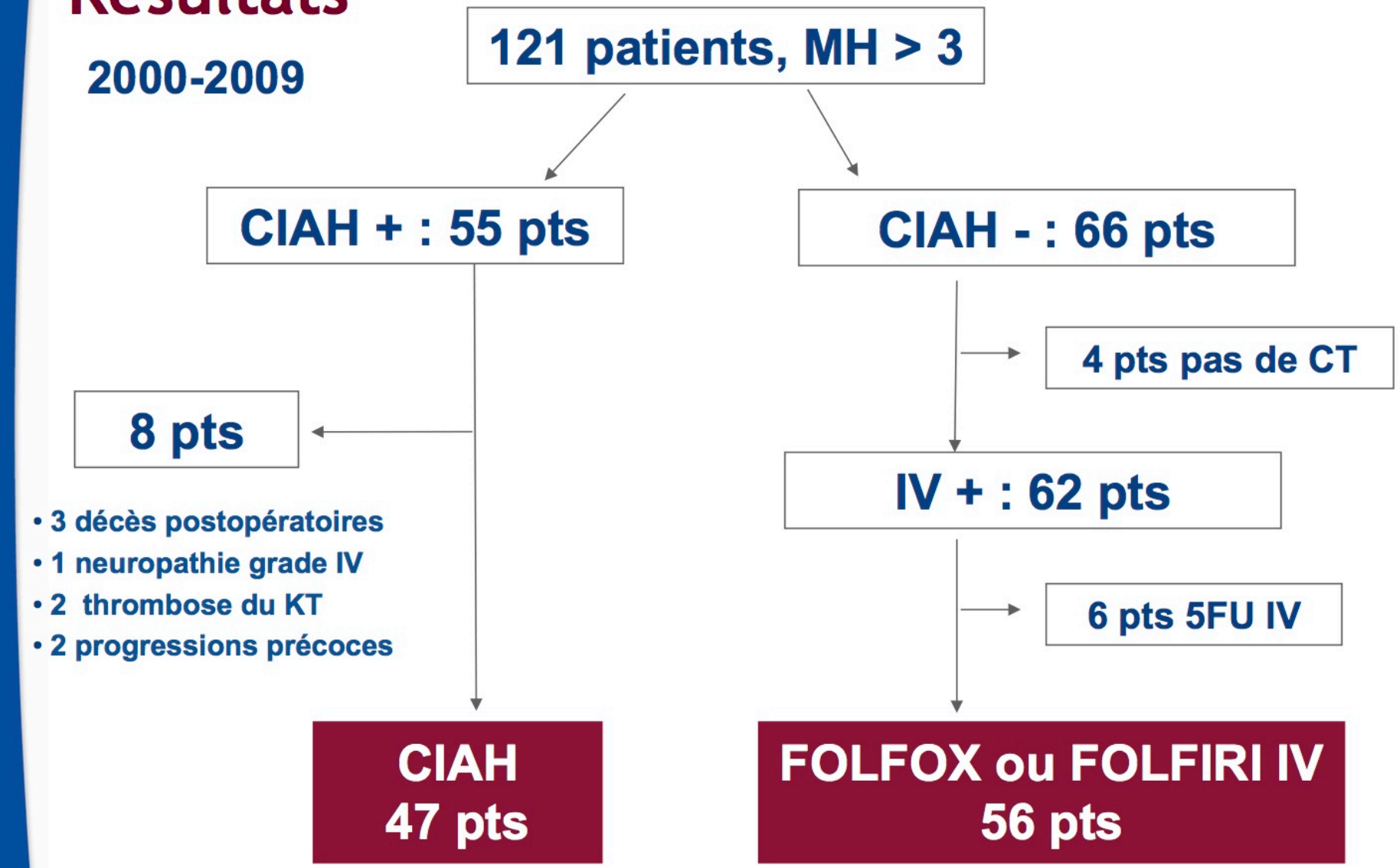
C. Honoré, D. Goéré, L. Benhaïm, S. Bonnet, JH. Lefèvre, F. Dumont, D. Malka, V. Boige, F. Maire, T. de Baere, D. Elias, M. Ducreux

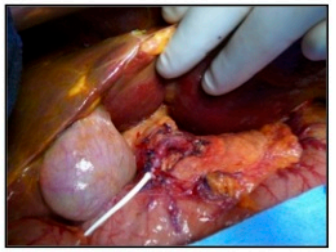
Goere, Ann Surg 2013; 257:114-120.

Institut de cancérologie GUSTAVE ROUSSY
VILLEJUIF - www.igr.fr

Résultats

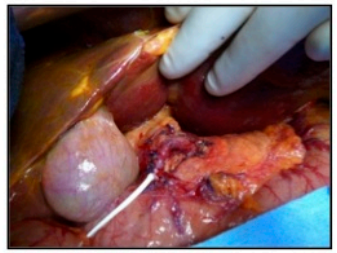
2000-2009



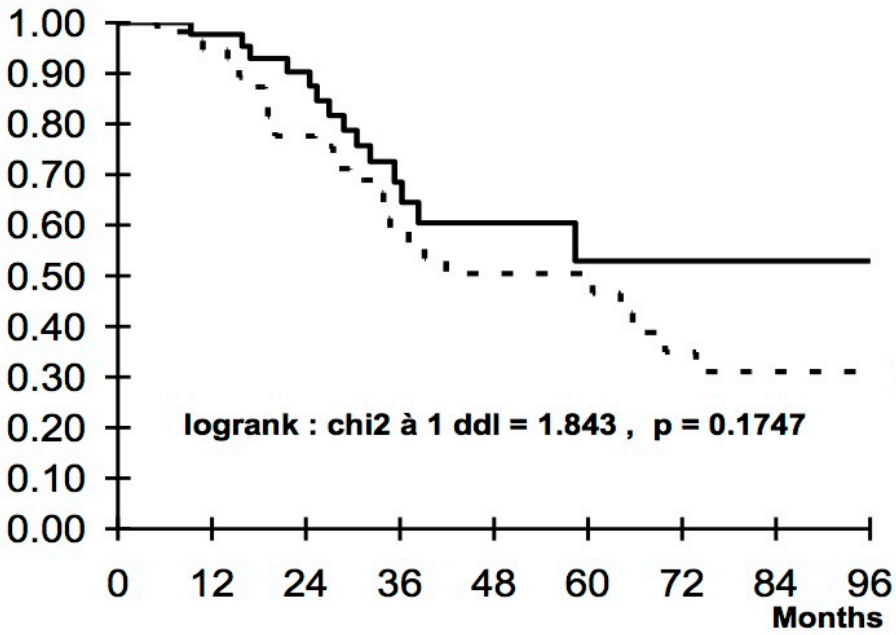


Résultats
Chimiothérapie intra-artérielle

- **Nombre de cures**
  - **29 (61%) ≥ 6 cures** — **Moyenne 8 ± 1,7**
  - **18 (38%) < 6 cures** — **Moyenne 3,2 ± 1,5**
- **Causes arrêt CIAH avant 6 cures**
  - **Toxicité systémique : 6 (13%)**
  - **Dysfonction KT : 6 (13%)**
  - **Récidive précoce : 5 (10%)** (2 hépatique, 3 extra-hépatique)
  - **Demande du patient : 1 (2%)**



Résultats
Survie globale



CIAH +

CIAH -

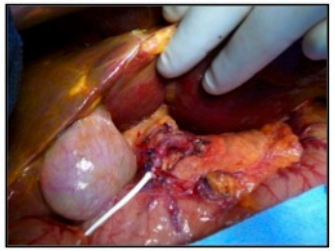
54% à 5 ans

40% à 5 ans

At risk

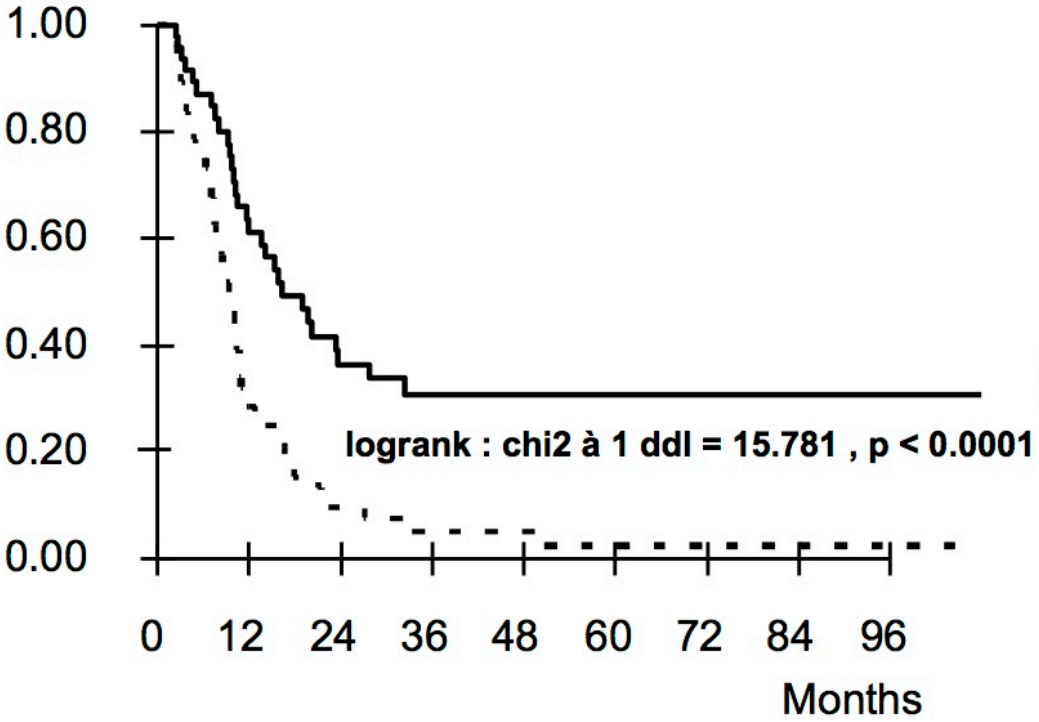
- ·	56	53	39	22	16	13	9	4	3
—	47	42	33	17	11	7	6	5	4

p NS



Résultats

Survie sans récidive



CIAH +

CIAH -

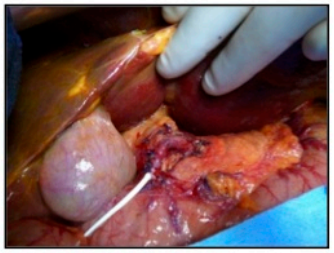
36% à 3 ans

5% à 3 ans

At risk

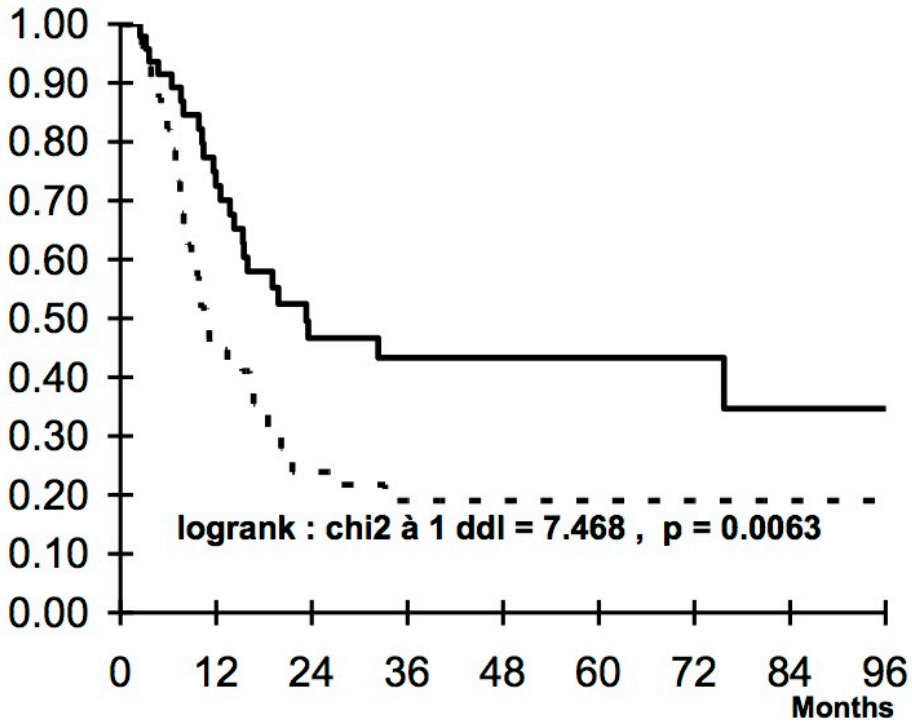
- ·	56	16	5	2	2	1	1	1	1
—	47	26	14	8	6	4	4	3	3

p<0,0001



Résultats

Survie sans récidive hépatique



CIAH +

CIAH -

43% à 3ans

20% à 3ans

p=0,0063

At risk

- ·	56	25	12	7	5	4	4	2	1
—	47	30	16	9	7	5	5	3	3

Palliative IA chemotherapy

ORIGINAL ARTICLES

Prolonged Survival of Initially Unresectable Hepatic Colorectal Cancer Patients Treated With Hepatic Arterial Infusion of Oxaliplatin Followed by Radical Surgery of Metastases

Diane Goéré, MD, Isabelle Deshaies, MD,* Thierry de Baere, MD, PhD,† Valérie Boige, MD,‡ David Malka, MD, PhD,‡ Frédéric Dumont, MD,* Clarisse Dromain, MD,† Michel Ducreux, MD, PhD,‡ and Dominique Elias, MD, PhD**

Annals of Surgery • Volume 251, Number 4, April 2010

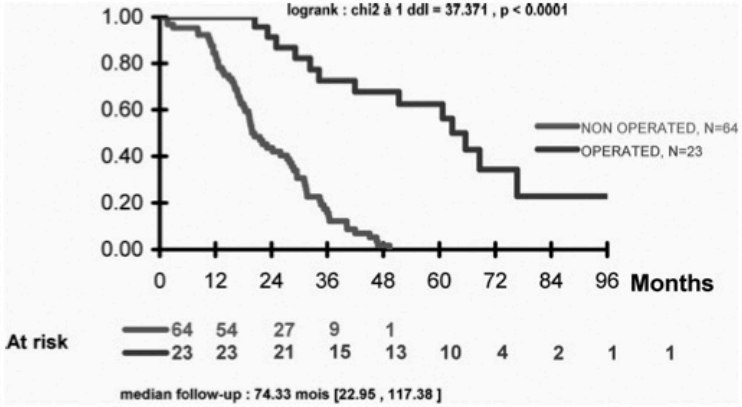


FIGURE 1. Overall survival of nonoperated (n = 64) and operated (n = 23) patients calculated from the date of diagnosis of liver metastases.

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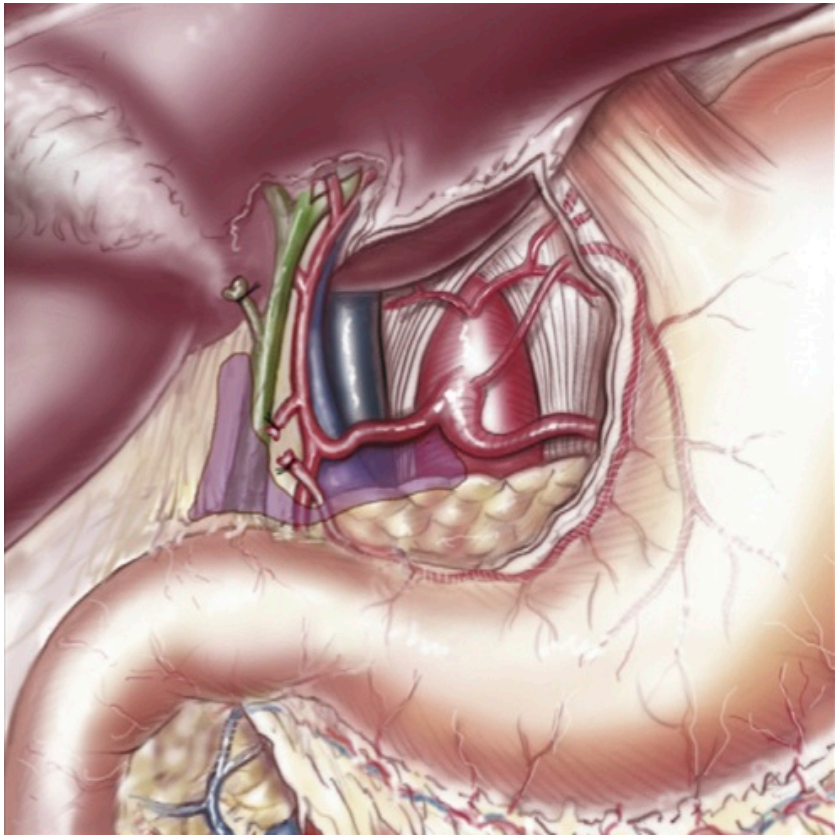
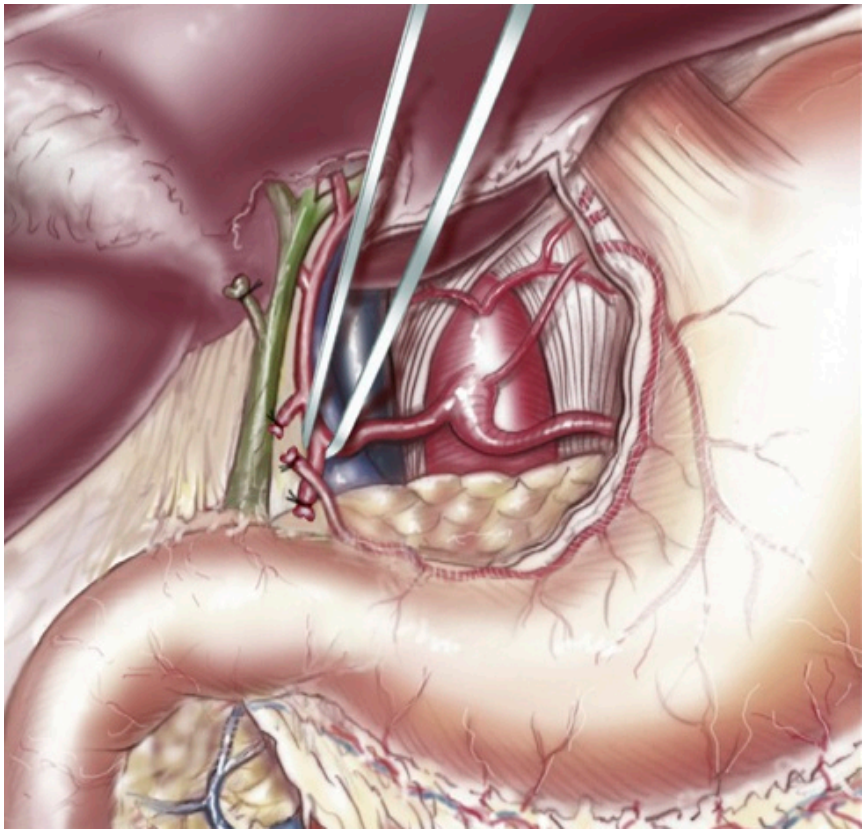
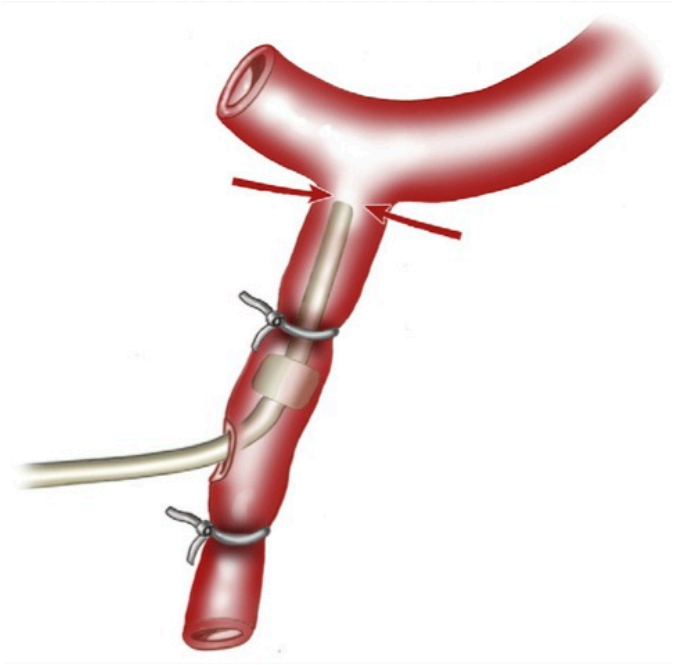
Intra-arterial chemotherapy

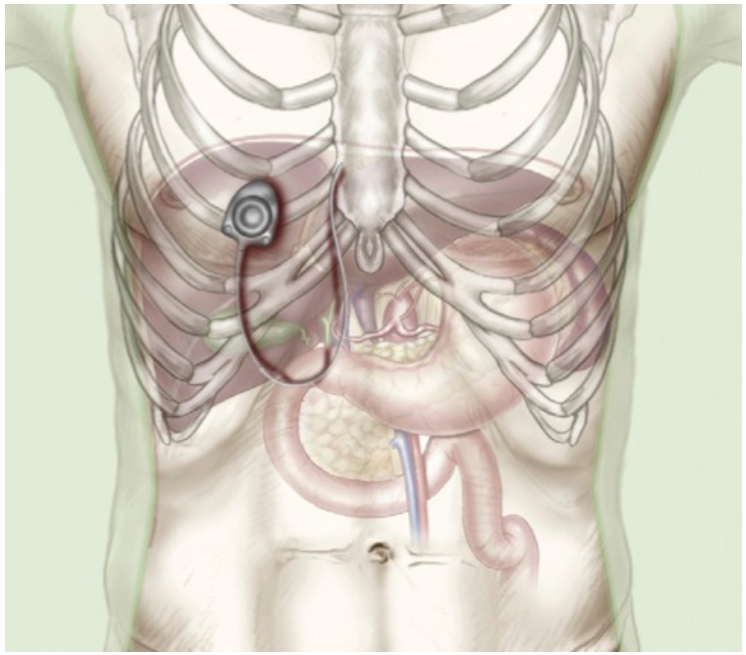
- ideal for multiple CRC MTST isolated to the liver
  - irresectable
  - after resection > 4 lesions
- Technically challenging
  - thrombosis
  - infection
- Placement: surgical or radiological

Surgical placement









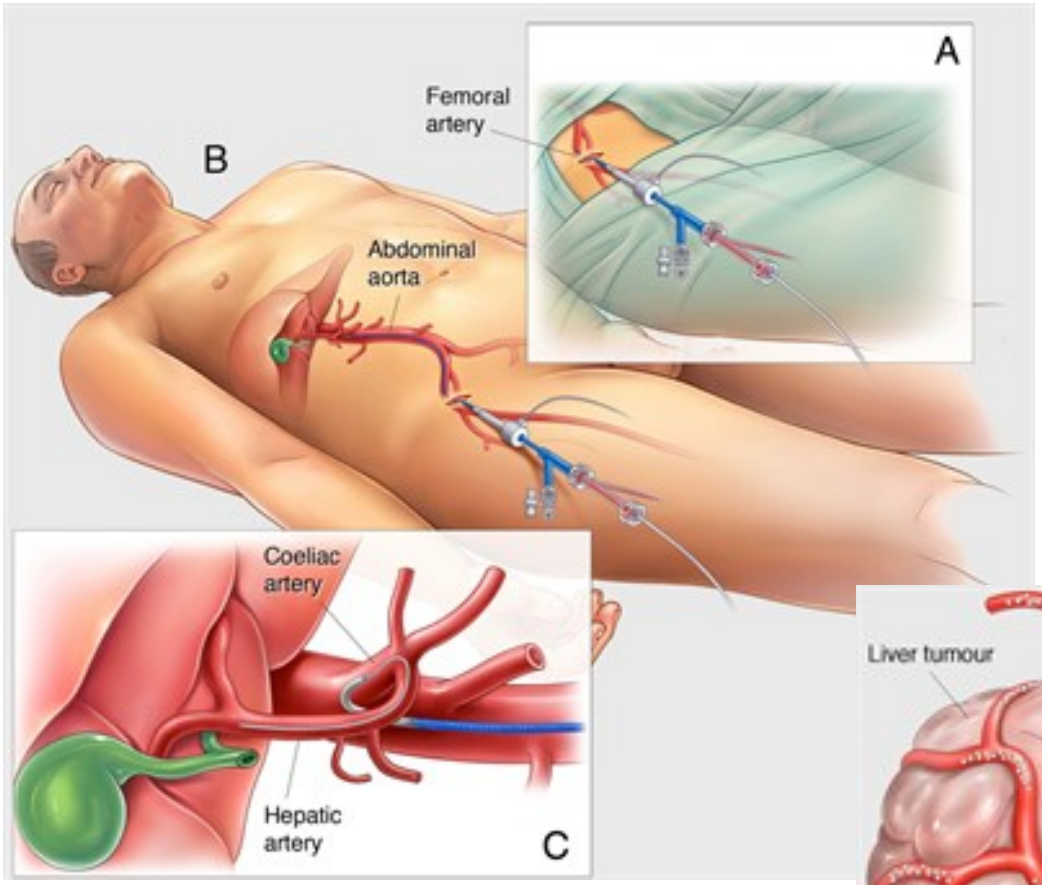
Intra-arterial chemotherapy

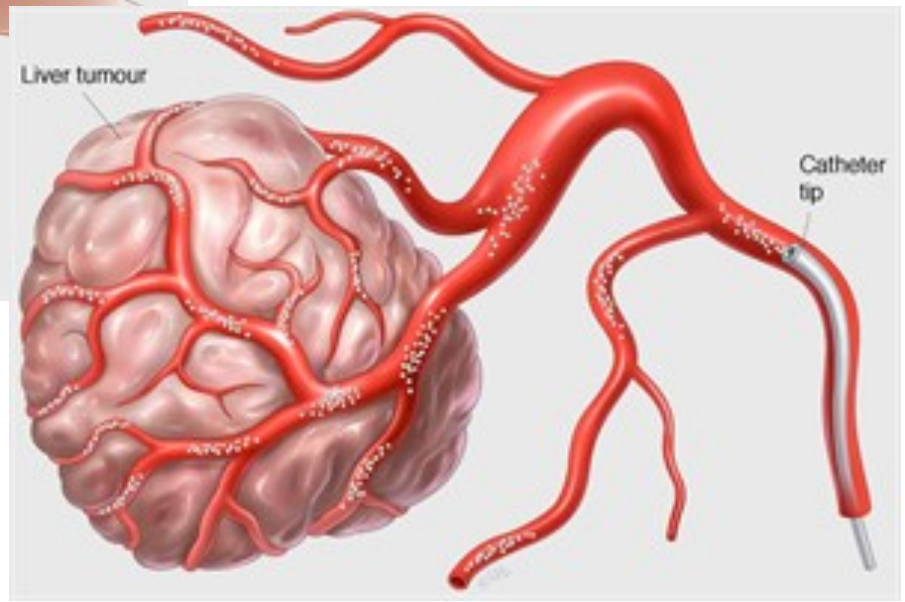
- Need for better prospective studies comparing modern IV and IA chemotherapy both in palliative and postoperative conditions

Yttrium-90 radioembolization

- TheraSpheres (20-30 microns)
- SIRSpheres (20-60 microns)

- First line therapy
- Second or third line chemotherapy
- Salvage for chemorefractory patients

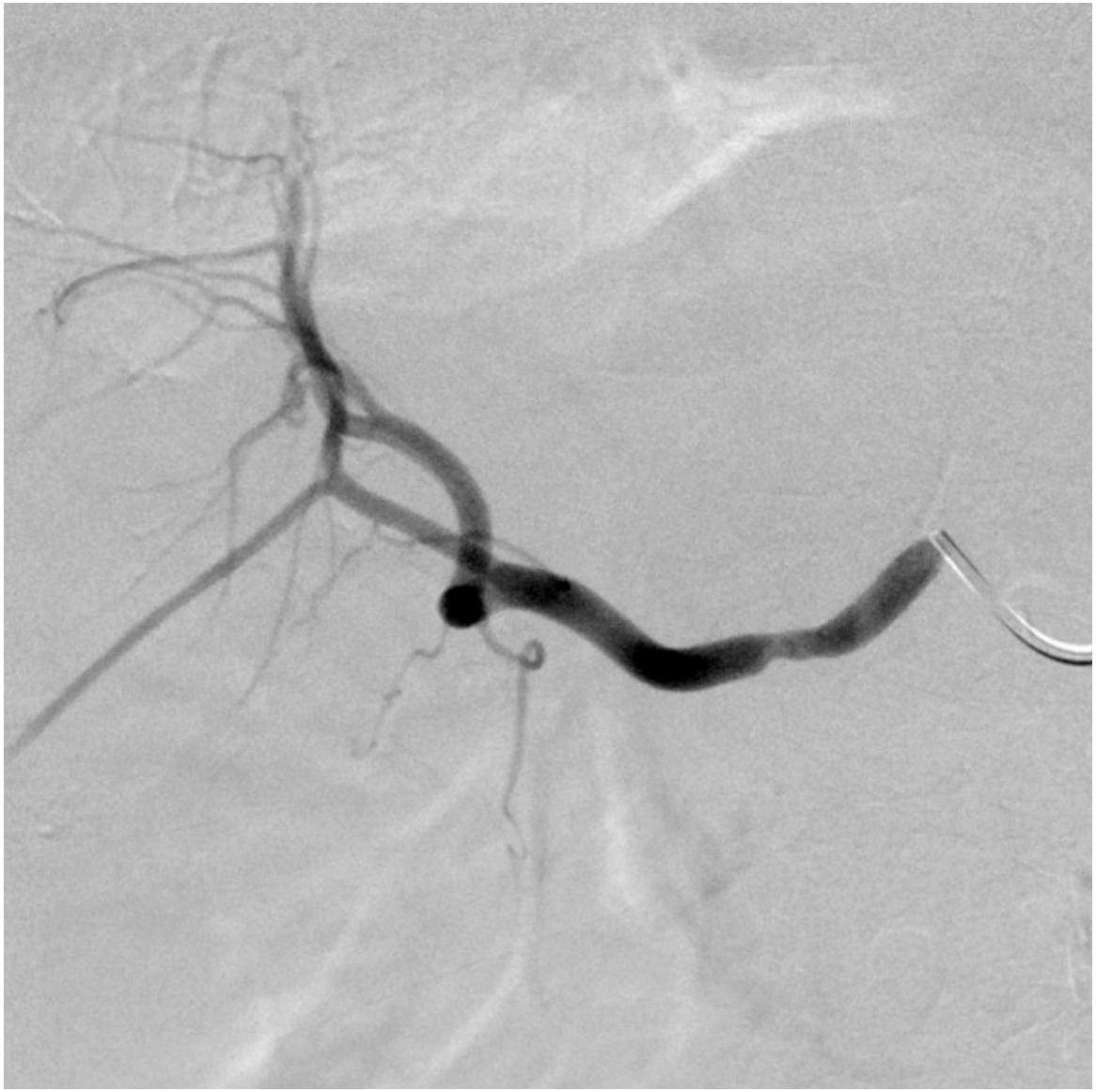

A
Femoral artery
B
Abdominal aorta
Coeliac artery
Hepatic artery
C


Liver tumour
Catheter tip

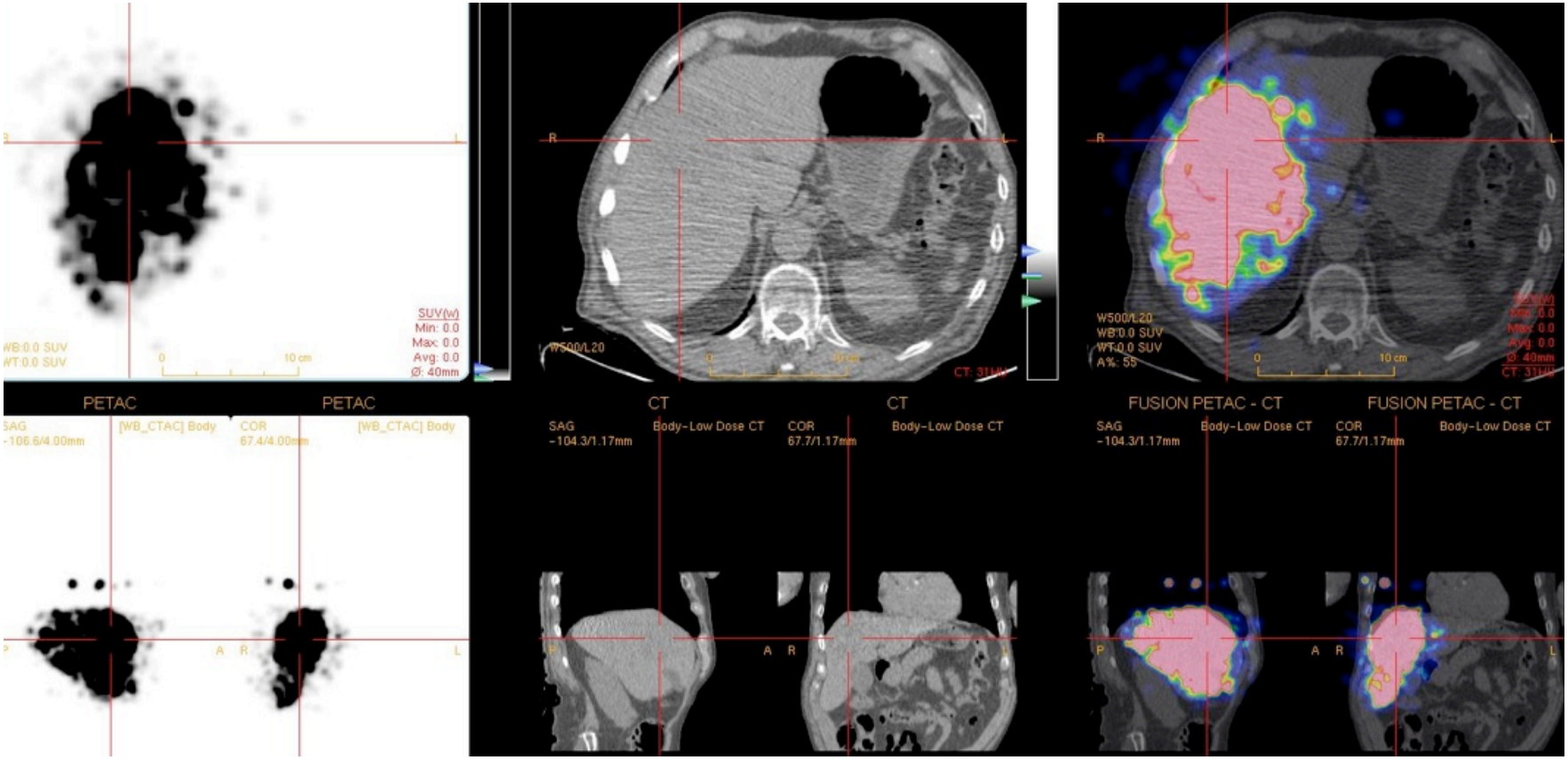
First-Line								
Gray[1]	74	SIR-Spheres† + FUDR HAC	LO	44%[W]	$P = 0.01$	8.3%	15.9 months[ΔL]	$P = 0.001$	39% at 2 yr	$P = 0.06$
		vs. FUDR HAC	LO	18%[W]		38.2%	9.7 months[ΔL]		29% at 2 yr	
van Hazel[2,3]	21	SIR-Spheres† + 5FU/LV	LD	90.1%*	$P < 0.001$	9.9%	18.6 months[Δ]	$P < 0.0005$	29.4 months	HR: 0.33 $P = 0.025$
		vs. 5FU/LV	LD	0%		60.0%	3.6 months[Δ]		12.8 months	
Sharma[4]	20	SIR-Spheres† + FOLFOX4	LD	90%		10%	9.3 months‡		nr	
			LO				14.2 months‡			
Kosmider[5]	19§	SIR-Spheres† + FOLFOX4 or 5FU/LV	LD	84%		5%	10.4 months‡		29.4 months	
			LO				10.7 months‡		37.8 months	
Tie[6]	31§	SIR-Spheres† + FOLFOX4 or 5FU/LV	LO	91%		9%	13.2 months‡		30.7 months	
			LO				16.4 months‡[L]			
phase II/III studies		FOLFOX4[7–10]			32–59%		7.6–9.0 months‡		16.2–19.5 months	
Consolidation of First-Line								
Sangro[11]	23§	SIR-Spheres†	LD	nr		nr	6.3[Tx]/11.2[Cx] months‡		16.8[Tx]/23.6[Cx] months‡	
Second- or Third-Line								
Lim[12]	30	SIR-Spheres† (+ 5FU)[70%]	LD	33%		27%	5.3 months[Δ]		nr	
van Hazel[13]	25	SIR-Spheres† + irinotecan	LD	48%		39%	6.0 months‡		12.2 months	
							9.2 months‡[L]			
phase II/III studies		irinotecan[14–17]		4–13%			2.6–4.3 months‡		6.4–10.0 months	
		FOLFIRI[18,19]		4–23%			2.5–4.7 months‡		10.5 months	
		irinotecan + cetuximab[15,20–22]		16–27%			3.2–4.0 months‡		8.6–10.7 months	
		panitumumab[23–26]		9–14%			1.8–3.2 months‡		6.3–9.3 months	

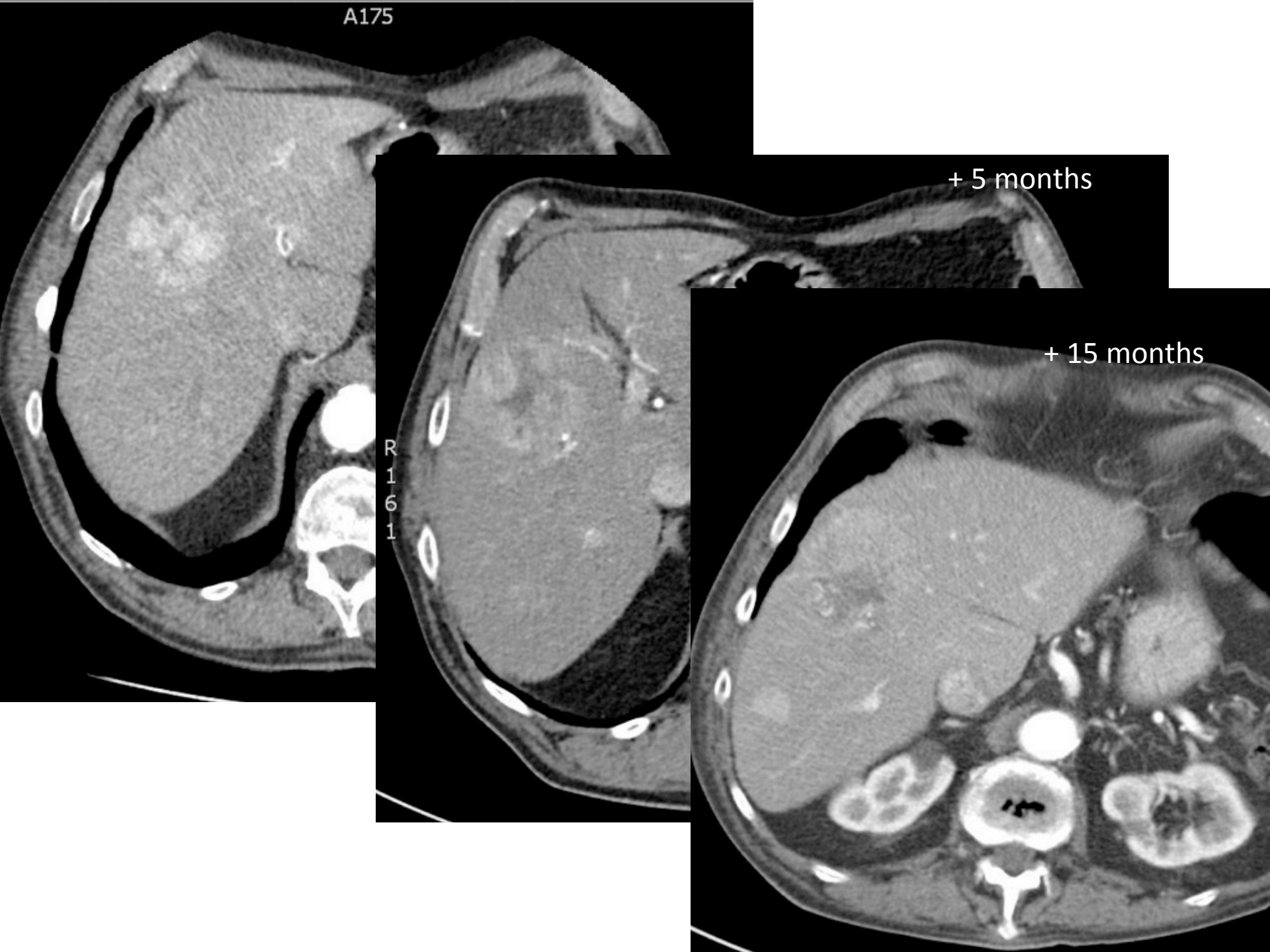
Salvage Therapy of Treatment-Refractory Disease

Hendlisz[27]	44	SIR-Spheres† + 5FU	LO	10%	76%	$P = 0.001$	5.5 months$^{\Delta L}$	HR: 0.38	10.0 months	ns
		vs. 5FU (> SIR-Spheres† at PD)	LO	0%	35%		2.1 months$^{\Delta L}$	$P = 0.003$	7.3 months	
Seidensticker[28]	29	SIR-Spheres†	LD	41.4%	17.2%		5.5 months‡	nr	8.3 months	HR: 0.26
	29	*vs.* BSC matched pairs	LD	nr	nr		2.1 months‡		3.5 months	$P < 0.001$
Bester[29]	224	SIR-Spheres†	LD	nr	nr		nr		11.9 months	HR: 0.50
	29	*vs.* conventional therapy or BSC	LD	nr	nr		nr		6.6 months	$P < 0.001$
Cosimelli[30]	50	SIR-Spheres†	LD	24%	24%		4 months‡		12.6 months	
Sofocleous[31]	19	SIR-Spheres†	LD		70.6%^{DCR}		6 months‡		16.0 months	
Kennedy[32]	606§	SIR-Spheres†	LD	nr	nr		nr		9.6 months	
Sofocleous[33]	18§	SIR-Spheres†	LD		40.0%^{DCR}		5.1 months‡		7.4 months	
Leoni[34]	51§	SIR-Spheres†	LD	24%^{c}			nr		8.0 months	
Nace[35]	51§	SIR-Spheres† (+ FUDR HAC)$^{33\%}$	LD	12.9%	64.5%				10.2 months	
			LO						17.0 months	
Cianni[36]	41§	SIR-Spheres†	LD	46%	36%		9.3 months‡		11.8 months	
Jakobs[37]	41§	SIR-Spheres†	LD	17%	61%		5.9 months$^{\Delta L}$		10.5 months	
Kennedy[38]	208§	SIR-Spheres†	LD	35.5%^{W}	55%		nr			
		responders							10.5 months	$P = 0.0001$
		non-responders & historical controls							4.5 months	



Selective treatmetn of the right liver MTST

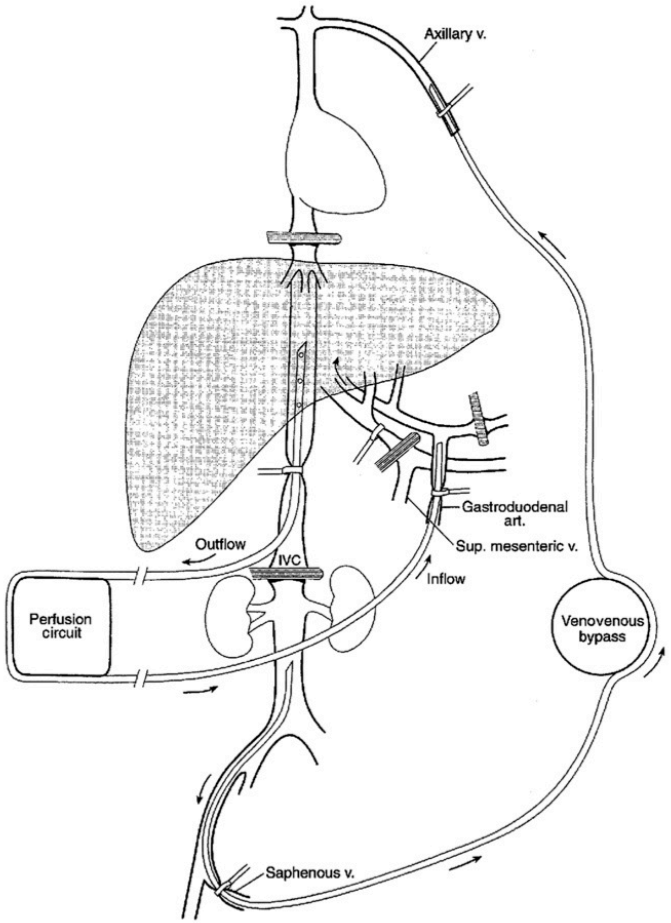



A175
+ 5 months
R
1
6
1
+ 15 months

Isolated liver perfusion

- High concentration of chemotherapy
- High temperature

- melphalan + TNF-α
- oxaliplatin



Duration	1 h
Hepatic tissue temp	39.5–40°C
Tumor necrosis factor#	1.0 mg
Melphalan	1.5 mg/kg
Flow rate	600–1200 ml/min
Arterial line pressure	110–200 mmHg*
Veno-venous bypass flow	1.8–2.0 l/min
Perfusate volume	
Perfusate composition	700 cm^3 crystalloid
	300 cm^3 packed red blood cells
	2000 U heparin
	20–40 meq $NaHCO_3$
Post perfusion flush	
Hepatic artery	1.5 l crystalloid
	1.5 l colloid
Portal vein	1.0 l crystalloid

#Not used currently
*Measured pressure in circuit, actual delivered pressure into hepatic artery is lower.

- Ocular melanoma MTST
- Neuro-endocrine MTST
- CRC MTST

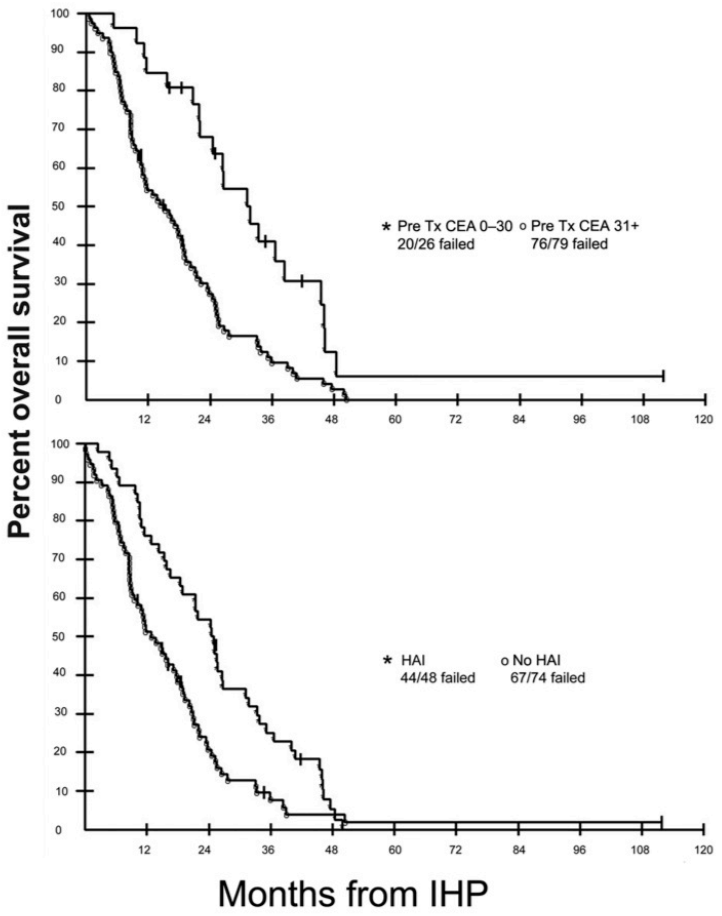


Figure 4. Actuarial overall survival in 120 patients with diffuse colorectal cancer liver metastases who underwent isolated hepatic perfusion (IHP) based on baseline carcinoembryonic antigen (CEA) level (top panel) or with or without hepatic artery infusion (HAI) therapy (bottom panel) following IHP. Tx, treatment.

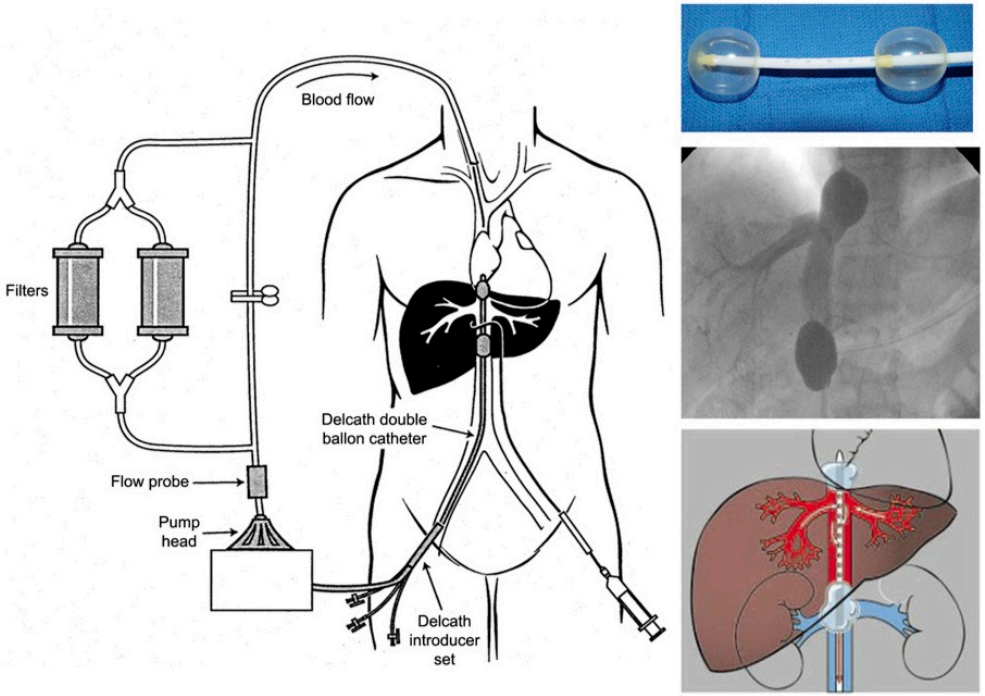


Figure 6. Diagram of the Delcath Catheter System. Melphalan is administered directly into the hepatic artery through an infusion catheter placed percutaneously via the femoral artery. Hepatic venous outflow is isolated via a double balloon catheter in the retrohepatic inferior vena cava (IVC) (shown top right). Blood is drawn out of the retrohepatic IVC through multiple fenestrations located along the length of the catheter between the cranial and caudal balloons. The blood is then pumped through a pair of activated charcoal filters prior to return to the systemic circulation via an internal jugular vein catheter. Fluoroscopic image of the isolated, retrohepatic IVC segment obtained by retrograde injection of contrast through the intraballoon fenestrations to confirm the absence of systemic leak is shown in the middle right.

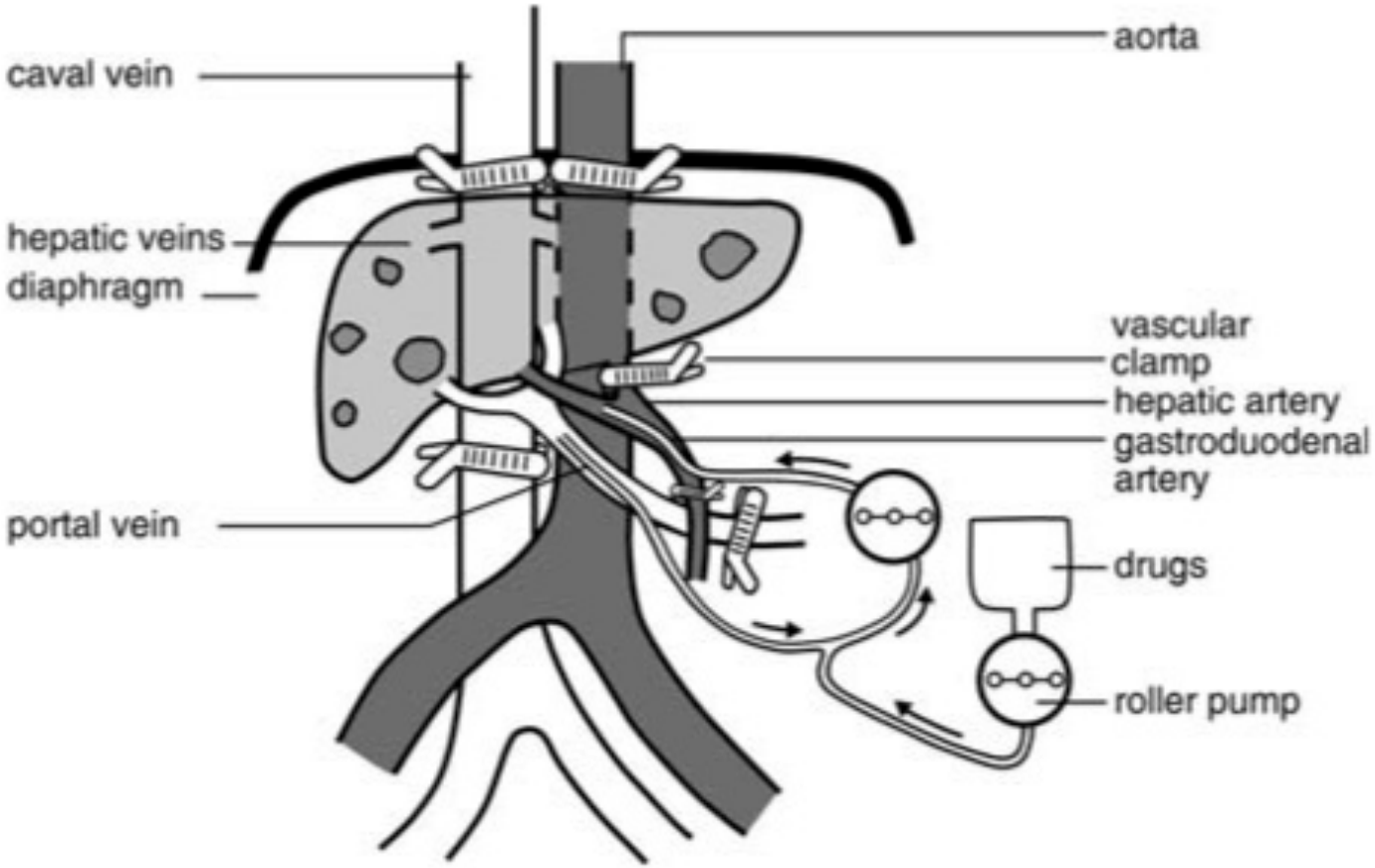
Annals of Surgical Oncology **15**(5):1367–1374
DOI: 10.1245/s10434-007-9714-z

Isolated Hypoxic Hepatic Perfusion with Retrograde Outflow in Patients with Irresectable Liver Metastases; A New Simplified Technique in Isolated Hepatic Perfusion

Cornelis Verhoef, MD,[1] Johannes H. W. deWilt, MD, PhD,[1] Flavia Brunstein, MD, PhD,[1] Andreas W. K. S. Marinelli, MD, PhD,[1] Boudewijn vanEtten, MD, PhD,[1] Maarten Vermaas, MD,[1] Gunther Guetens, PhD,[2] Gert de Boeck, PhD,[2] Ernst A. de Bruijn, PhD,[2] and Alexander M. M. Eggermont, MD, PhD[1]

[1]Department of Surgical Oncology, Erasmus University Medical Centre—Daniel den Hoed Cancer Centre, PO Box 5201, 3008 AE, Rotterdam, The Netherlands
[2]Laboratory of Experimental Oncology, University of Leuven—UZ Gasthuisberg, CDG building, Herestraat 49, B-3000, Leuven, Belgium

Isolated liver perfusion



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DOI 10.1245/s10434-008-0179-5

Annals of
SURGICAL ONCOLOGY
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ORIGINAL ARTICLE – HEPATOBILIARY AND PANCREATIC TUMORS

A Phase I Study of Hyperthermic Isolated Hepatic Perfusion with Oxaliplatin in the Treatment of Unresectable Liver Metastases from Colorectal Cancer

Herbert J. Zeh III, MD[1], Charles K. Brown, MD, PhD[1], Matthew P. Holtzman, MD[1], Merrill J. Egorin, MD[2,3], Julianne L. Holleran, BS[2], Douglas M. Potter, PhD[4], and David L. Bartlett, MD[1]

[1]Division of Surgical Oncology, Department of Surgery, University of Pittsburgh School of Medicine, Suite 417 UPMC Cancer Pavilion, 5150 Center Ave., Pittsburgh, PA 15232, USA; [2]Molecular Therapeutics/Drug Discovery Program, University of Pittsburgh Cancer Institute, Pittsburgh, PA 15232, USA; [3]Division of Hematology/Oncology, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA 15232, USA; [4]Biostatistics Department, Graduate School of Public Health and Biostatistics Facility, University of Pittsburgh Cancer Institute, University of Pittsburgh, Pittsburgh, PA 15213, USA

TABLE 1 Oxaliplatin dose escalation scheme

Dose level	Oxaliplatin dose (mg/m^2)	Planned number of patients	Actual number of patients enrolled
1	5	1	1
2	10	1	1
3	20	1	1
4	40[a]	3–6	6
5	60	3–6	1[b]
6	90	3–6	0
7	120	3–6	0
8	150	3–6	0

[a] MTD

[b] DLT of grade V VOD and fulminant hepatic failure

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YES!

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CHU Liège, Université de Liège

Thanks!

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