Locoregional Treatments of Colorectal Liver Metastases

David Malka, MD, PhD
Department of Cancer Medicine
Gustave Roussy – Villejuif
France

Hepatic Arterial Infusion of chemotherapy (HAI)

Radioembolisation (RE)

TransArterial ChemoEmbolisation (TACE)

Hepatic Arterial Infusion of chemotherapy (HAI)

Radioembolisation (RE)

TransArterial ChemoEmbolisation (TACE)

HAI: rationale

- Colorectal cancer (CRC): liver is usually the 1st site of mets

  - Hematogenic spread: portal vein → liver → lung → other organs (1541 CRC necropsies [1])

→ *Eradicate colorectal liver metastases (CRLM) by locoregional treatments (surgery, RFA, HAI,…) may limit extrahepatic metastatic spreading*

[1] Weiss L, *et al*. *J Pathol* 1986;150:195-203

HAI: rationale

- **Vascularization**

Animal models[1]

- CRLM: almost exclusively by *hepatic artery* (e.p. if > 3 cm)
- Normal liver: preferentially by *portal vein*

Clinical study with labelled floxuridin (FUDR) [2]

- $[FUDR]_{hepatocytes}$: similar after HAI or intraportal (IP) infusion
- $[FUDR]_{tumor}$: 12,4 vs 0,8 mg/l (p = 0,01)

Randomized trial, HAI *vs* IP CTx for CRLM [3]

- ORR IP: 0% (33% after *crossover* to HAI)
- ORR HAI (same dose): 33%

→ *HAI: selectively targets CRLM while relatively sparing normal liver*

[1] Breedis C, Young C. *Am J Pathol* 1954;30:969-

[2] Sigurdson ER, *et al*. *J Clin Oncol* 1987;5:1836-40

[3] Daly JM, *et al*. *Arch Surg* 1987;122:1273-7

HAI: rationale

- **Resection (e.p. 2^{ary}): e.p. liver-only (or liver-dominant) CRLM**

→ HAI: logical in case of (potentially) resectable CRLM

HAI: rationale

- **The therapeutic armamentarium of mCRC remains limited**

  - ➔ No new cytotoxic agent since mid-90'
  - ➔ Regorafenib: the only new targeted agent since mid-00'

  ➔ HAI: mandatory in the relentless efforts to optimize available anticancer drugs

HAI: rationale

Drug	Half-life	Increased Exposure by HAI (fold Increase)
FUDR	<10 min	100–400
5-fluorouracil	10 min	5–10
Bischlorethylnitrosurea	<5 min	6–7
Mitomycin C	≤10 min	6–8
Oxaliplatin	15–19 h	4–5

HAI: systemic toxicity

	FUDR	Oxaliplatine
Increased exposure by HAI (vs IV)	100-400	4-5
Systemic AE	+/-	+
Hepatobiliary AE	++	+

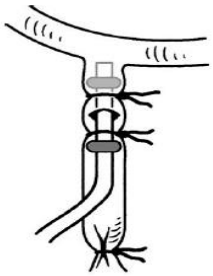
- FUDR: ~ 0! (hepatic extraction: 94-99%)
- Oxaliplatin
  - Non-negligible (systemic diffusion ~ 50%)
  - Hematological toxicity: ~ IV
  - Neurotoxicity: ~ IV

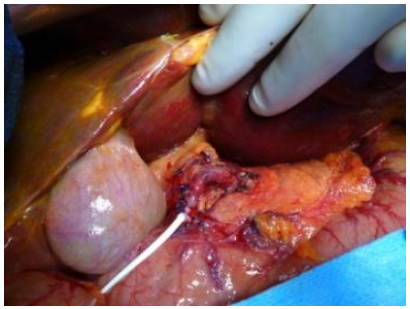
Burtin P, et al. JFHOD 2010

HAI: procedures

1. Surgery

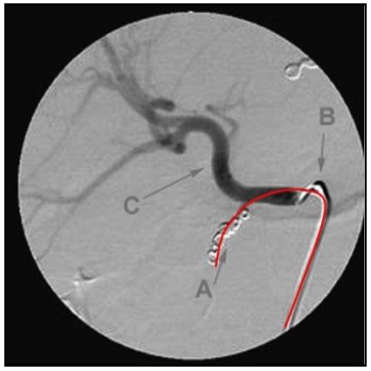
- Catheter inserted during surgical procedures
- Mostly into the gastroduodenal artery (GDA)
- Connected to port system placed onto right costal arc

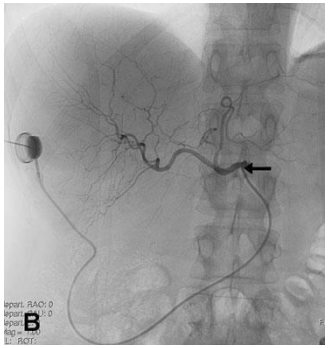


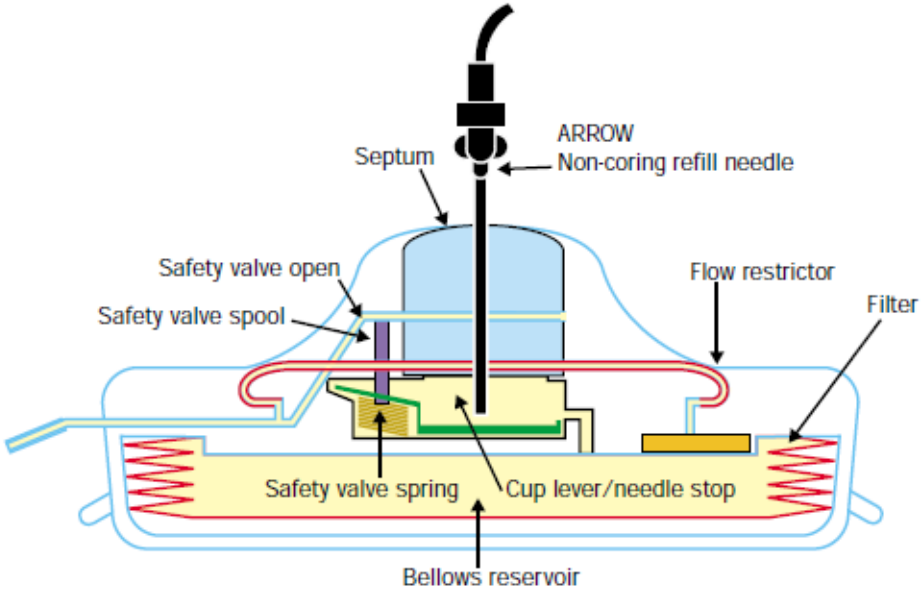


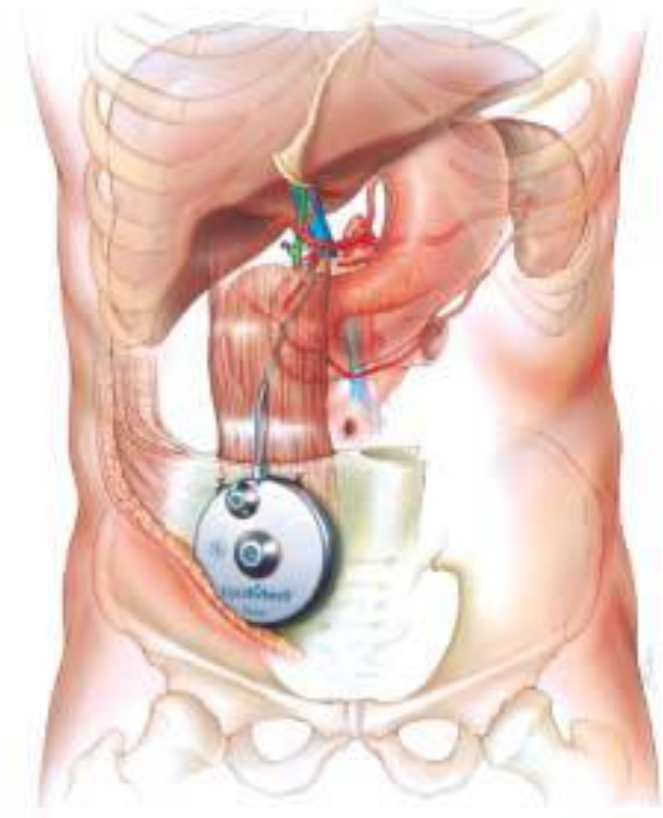
2. Mini-invasive: interventional radiology

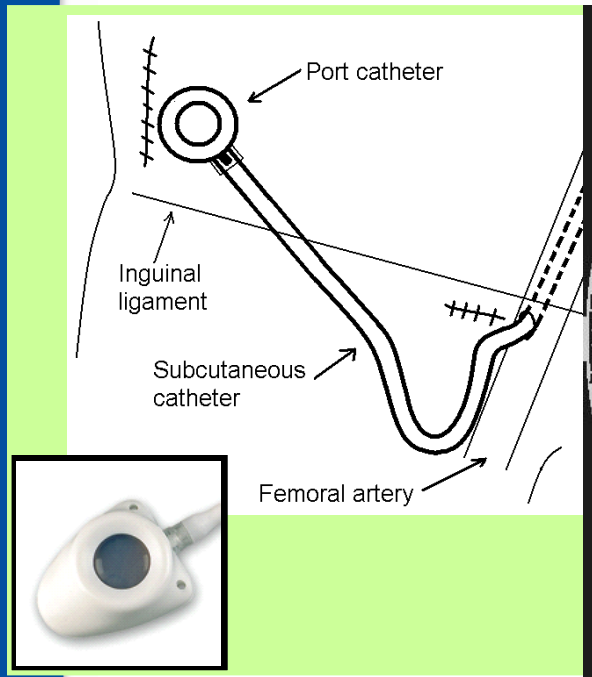
- Transfemoral
- Angiography
- Catheter inserted into the GDA
- GDA obstructed by coils, KT blocked
- Lateral holes of the KT placed into the common hepatic artery
- Branches to duodenum and lower 1/3 of stomach are embolized

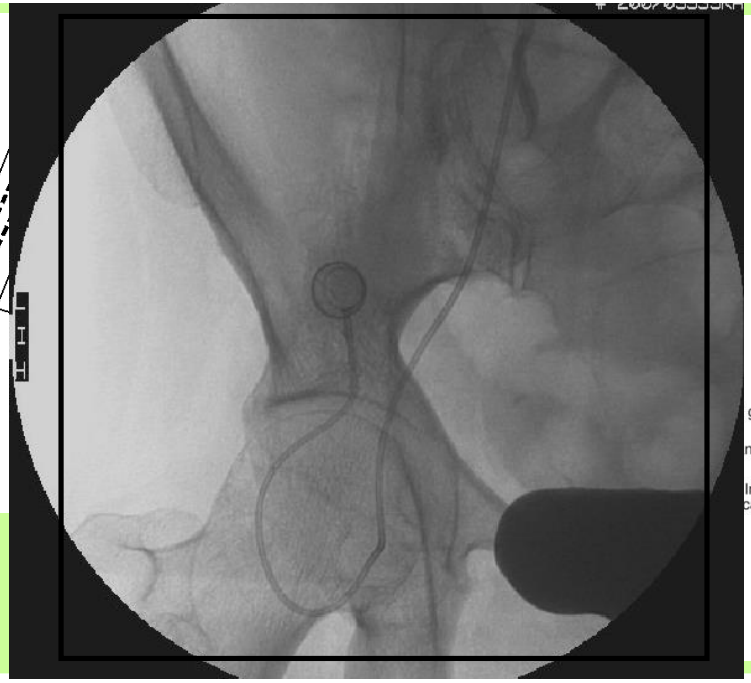


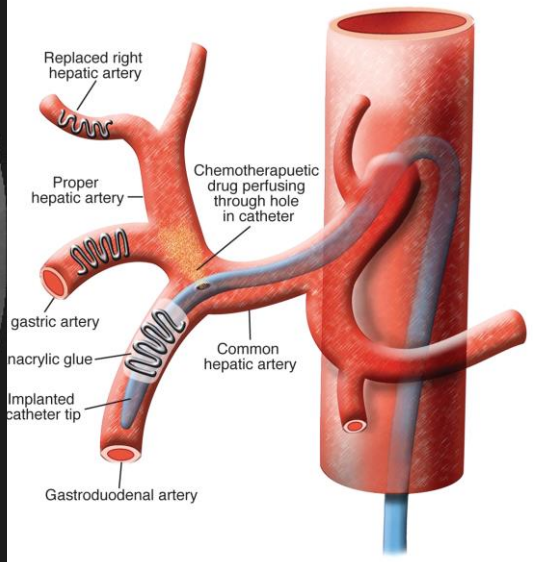



ARROW
Non-coring refill needle
Septum
Safety valve open
Safety valve spool
Flow restrictor
Filter
Safety valve spring
Cup lever/needle stop
Bellows reservoir




Port catheter
Inguinal ligament
Subcutaneous catheter
Femoral artery




Replaced right hepatic artery
Proper hepatic artery
Chemotherapuetic drug perfusing through hole in catheter
gastric artery
nacrylic glue
Common hepatic artery
Implanted catheter tip
Gastroduodenal artery

HAI: complications

Systematic review (1950-2001, 101 studies, 4580 patients)

- Mortality: 1%
- Morbidity
  - Gastrointestinal: 22% (e.p. 5FU)
  - Hepatitis: 19%, biliary toxicity (e.p. FUDR)
  - Hematotoxicity: 8% (e.p. 5FU)
  - HA Obstruction: 6%
  - HAI catheter thrombosis: 5%
  - HAI catheter migration: 7%

Barnett KT, Malafa MP. *Int J Gastrointest Cancer* 2001;30:147-60

Palliative HAI

Fluoropyrimidine-HAI (hepatic arterial infusion) versus systemic chemotherapy (SCT) for unresectable liver metastases from colorectal cancer (Review)

Mocellin S, Pasquali S, Nitti D

THE COCHRANE COLLABORATION®

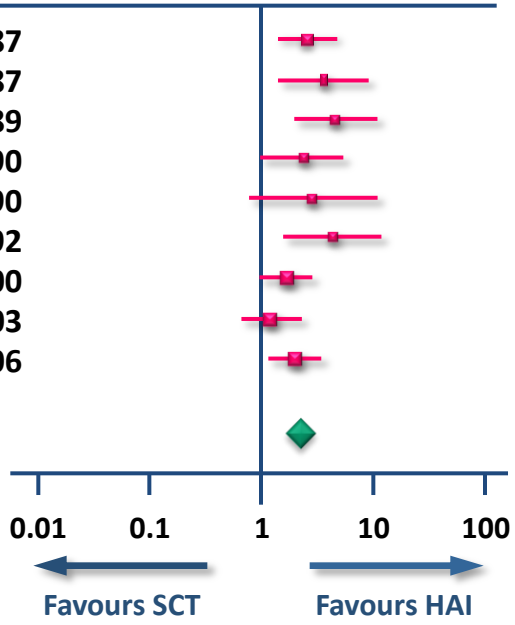
Palliative HAI

Méta-analysis, Cochrane 2009 (10 trials)

Forest plot of risk ratio for **tumor response** (all trials).
HAI : hepatic arterial infusion – SCT : systemic chemotherapy

Study or Subgroup	HAI Events	HAI Total	SCT Events	SCT Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Kemeny 1987	24	45	10	48	12.0%	2.56 [1.38, 4.74]	1987
Chang 1987	13	21	5	29	5.2%	3.59 [1.51, 8.53]	1987
Hohn 1989	21	50	6	65	6.5%	4.55 [1.99, 10.42]	1989
Martin 1990	15	31	6	29	7.7%	2.34 [1.05, 5.20]	1990
Wagman 1990	17	31	2	10	3.7%	2.74 [0.76, 9.86]	1990
Rougier 1992	29	70	4	41	6.2%	4.25 [1.61, 11.22]	1992
Lorenz 2000	34	77	14	52	20.7%	1.64 [0.98, 2.74]	2000
Kerr 2003	17	77	20	108	20.6%	1.19 [0.67, 2.12]	2003
Kemeny 2006	28	59	14	58	17.5%	1.97 [1.16, 3.34]	2006
Total (95% CI)		461		440	100%	2.26 [1.80, 2.84]	
Total events	198		81				

Hererogeneity: $Chi^2 = 12.20$, $df = 8$ ($P = 0.14$); $I^2 = 34\%$
Test for overall effect: $Z = 7.03$ ($P < 0.00001$)



Mocellin S, et al. Cochrane Database System Rev 2009

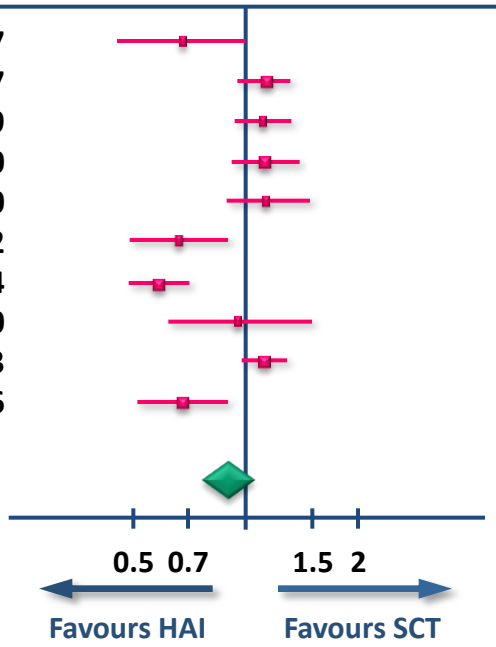
Palliative HAI

Méta-analysis, Cochrane 2009 (10 trials)

Forest plot of hazard ratio for **overall survival** (all trials).
HAI : hepatic arterial infusion – SCT : systemic chemotherapy

Study or Subgroup	Log [Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Kemeny 1987	-0.386	0.198	7.6%	0.68 [0.46, 1.00)	1987
Chang 1987	0.11	0.077	11.5%	1.12 [0.96, 1.30)	1987
Hohn 1989	0.107	0.0811	11.3%	1.11 [0.95, 1.30)	1989
Wagman 1990	0.1179	0.1002	10.8%	1.13 [0.92, 1.37)	1990
Martin 1990	0.1211	0.1204	10.1%	1.13 [0.89, 1.43)	1990
Rougier 1992	-0.406	0.152	9.1%	0.67 [0.49, 0.90)	1992
Allen 1994	-0.528	0.092	11.0%	0.59 [0.49, 0.71)	1994
Lorenz 2000	-0.0397	0.217	7.1%	0.96 [0.63, 1.47)	2000
Kerr 2003	0.112	0.0616	11.8%	1.12 [0.99, 1.26)	2003
Kemeny 2006	-0.386	0.135	9.7%	0.68 [0.52, 0.89)	2006
Total (95% CI)			100%	0.90 [0.76, 1.07]	

Hererogeneity: $Tau^2 = 0.06$, $Chi^2 = 60.83$, df = 9 (P < 0.00001); $I^2 = 85\%$
Test for overall effect: Z = 1.17 (P = 0.24)



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

Mocellin S, et al. Cochrane Database System Rev 2009

Palliative HAI

Essais randomisés en 2011 (n = 10)							
First Author	Treatment Arms	N	Response Rate (%)	p	Median survival (mo)	p	Design flaws
Kemeny[30]	HAI FUDR SYS FUDR	48 51	53 21	.001	17 12	NS	Cross-over allowed (60% crossed over)
Chang[28]	HAI FUDR SYS FUDR	32 32	62 17	.003	17 12	NS	Extrahepatic disease, dose of HAI FUDR
Hohn[29]	HAI FUDR SYS FUDR	67 76	42 9	.001	16.5 15.8	NS	Extrahepatic disease, cross-over allowed
Martin[34]	HAI FUDR SYS 5-FU	39 35	48 21	.02	12.6 1.5	NS	Extrahepatic disease, dose of HAI FUDR
Wagman[36]	HAI FUDR SYS FUDR	31 10	55 20	NR	13.8 11.6	NS	Cross-over allowed
Rougier[35]	HAI FUDR SYS 5-FU or BSC	81 82	41 9	NR	15 11	<.02	Dose of HAI FUDR
Allen-Mersh[27]	HAI FUDR SYS 5-FU or BSC	51 49	NR NR	NR	13.5 7.5	.03	
Lorenz[33]	HAI FUDR HAI 5-FU + LV	54 57	43 45	.019	12.7 18.7	NS	Ports used, cross-over allowed, dose adjustment of HAI FUDR
Kerr[32]	SYS 5-FU + LV HAI 5-FU + LV SYS 5-FU + LV	57 145 145	27 22 19	NS	17.6 14.7 14.8	NS	Ports used, FUDR not used for HAI
Kemeny[31]	HAI FUDR + Dex SYS 5-FU + LV	68 67	47 24	.02	24.4 20	.003	

Abbrevations: HAI, hepatic artery infusion; SYS, systemic infusion; 5-FU, 5-fluorouracil; FUDR, floxuridine; BSC, bischlorethylnitrosurea; NS, not significant; NR, not reported.

- **HAI (FU/FUDR) : ↗ ORR(41-62% IAH vs. 9-27% IV) – ↗ OS?**

Ammori JB, Kemeny NE. Semin Oncol 2010;37:139-48

Palliative HAI

AHI oxaliplatin + iv LV5FU2 1st-2nd line

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Hepatic Arterial Oxaliplatin Infusion Plus Intravenous Chemotherapy in Colorectal Cancer With Inoperable Hepatic Metastases: A Trial of the Gastrointestinal Group of the Fédération Nationale des Centres de Lutte Contre le Cancer

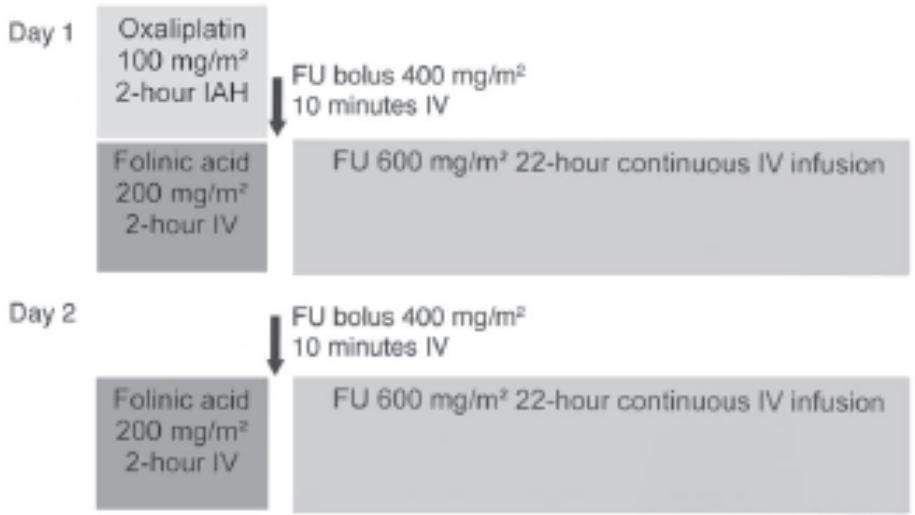
Michel Ducreux, Marc Ychou, Agnès Laplanche, Erick Gamelin, Philippe Lasser, Fares Husseini, François Quenet, Frédéric Viret, Jacques-Henri Jacob, Valérie Boige, Dominique Elias, Jean-Robert Delperro, and Monique Luboinski

Ducreux M, et al. J Clin Oncol 2005;23:4881-7

Palliative HAI
Phase II trial

- 1999-2001
- 6 centres
- Inclusion criteria
  - Non-resectable CRLM
  - No extrahepatic disease
  - Oxaliplatin-naïve

HAI oxaliplatin + iv LV5FU2



Ducreux et al, J Clin Oncol 2005

Hepatic Arterial Oxaliplatin Infusion Plus Intravenous Chemotherapy in Colorectal Cancer With Inoperable Hepatic Metastases: A Trial of the Gastrointestinal Group of the Fédération Nationale des Centres de Lutte Contre le Cancer

- N = 28 patients (21: 2nd line)
- Advanced disease
  - > 4 CRLM = 68%
  - Bilobar = 68%
- No biliary toxicity

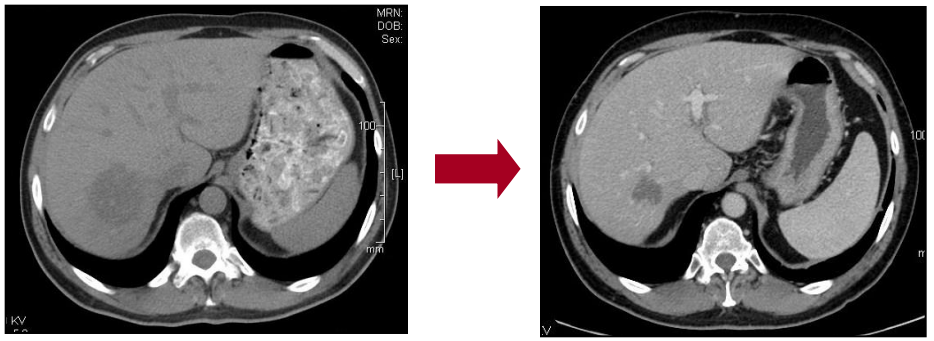
Toxicity	All Grades		Grade 3 to 4	
	No. of Patients	%	No. of Patients	%
Nausea and vomiting	19	73	1	4
Diarrhea	16	62	2	8
Neurotoxicity	18	69	1	4
Leukopenia	14	54	4	15
Neutropenia	18	69	10	38
Thrombopenia	12	46	3	12
Mucositis	11	42	1	4
Infection	6	23	—	—

- Median number HAI cycles = 8 [0-20]

ORR: 64%

5 surgical resections

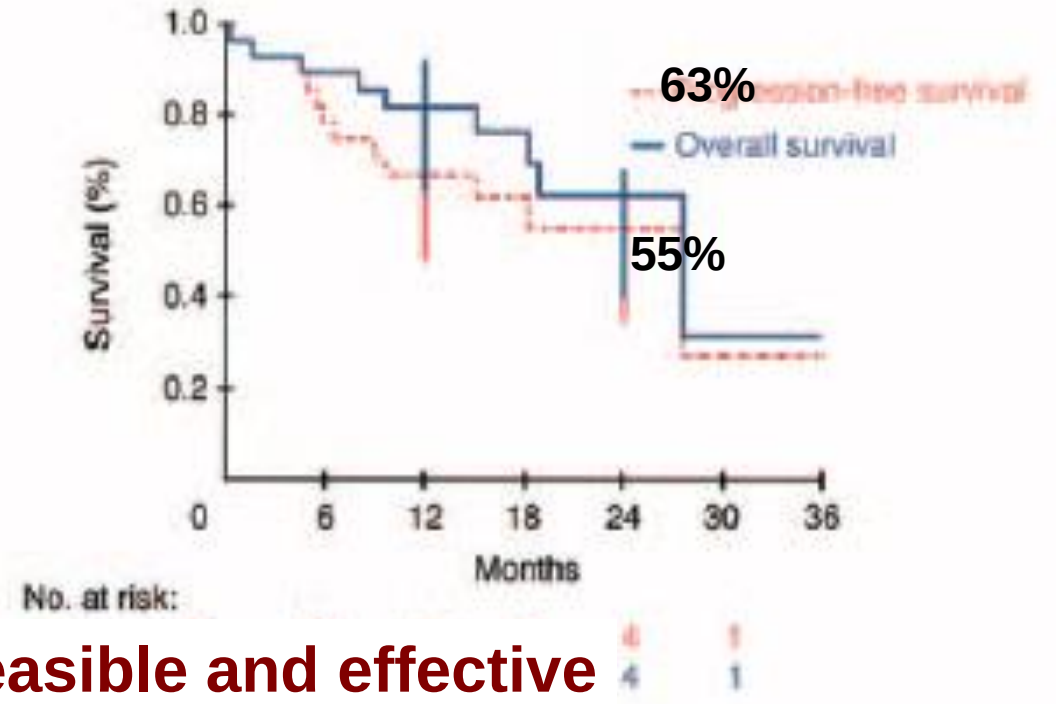
Extrahepatic PD: 8 pts



Follow-up: 23 months

PFS: 27 months

OS: 27 months



=> HAI Oxaliplatin: feasible and effective

Palliative HAI

HAI oxaliplatin + iv LV5FU2 ≥ 2nd line

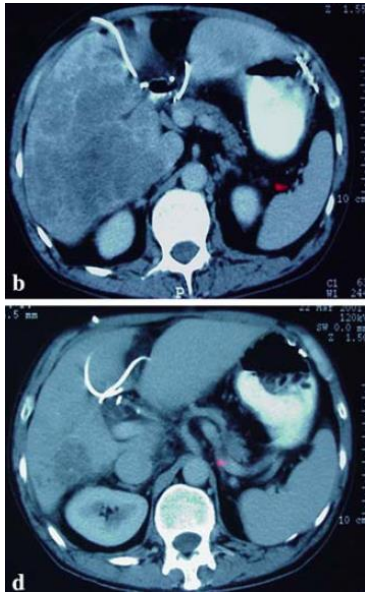
Hepatic Arterial Infusion of Oxaliplatin and Intravenous LV5FU2 in Unresectable Liver Metastases from Colorectal Cancer after Systemic Chemotherapy Failure

Valérie Boige, MD,[1] David Malka, MD, PhD,[1] Dominique Elias, MD, PhD,[2] Marine Castaing, MS,[3] Thierry De Baere, MD,[4] Diane Goere, MD,[2] Clarisse Dromain, MD,[4] Marc Pocard, MD, PhD,[2] and Michel Ducreux, MD, PhD[1]

Boige V, et al. Ann Surg Oncol 2008;15:219-26

- 2000-2004
- N=44
- Nb cycles = 9 [0-25]

Characteristics	$n = 44$
5-FU / LV only	1
FOLFIRI (only)	37 (9)
FOLFOX (only)	34 (6)
FOLFOX and FOLFIRI	28



- ORR =62%

Response	Patients ($n = 39^a$)
Complete response (%)	0 (0)
Partial response (%)	24 (62)
Stable disease (%)	10^b (26)
Tumor disease control (%)	34 (87)
Progressive disease (%)	5 (13)

⇒ HAI Oxaliplatin: feasible and effective after systemic chemotherapy failure, even after systemic oxaliplatin

Boige et al, Ann Surg Oncol 2007

Palliative HAI

HAI oxaliplatin + iv V5FU2 all lines

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**

Goéré D, et al. Ann Surg 2010;251:686-91

- N= 87
- Non resectable CRLM
- HAI Oxaliplatin + IV 5-FU
- Chemotherapy-naive: 18 (21%)
- N cycles: 8 [0-25]

23 patients (26%): CRLM resection

21 curative resections

CRCLM Characteristics	Nonoperated N = 64	Operated N = 23	*P*
Synchronous	54	20	0.96
Recurrence	14	5	0.78
Bilateral	59	19	0.37
Number—median (range)	8 (1–60)	5 (1–38)	0.22
Size—median (range) mm	50 (10–150)	53 (24–140)	0.88

HAI: initial treatment in 43% of operated pts vs. 14% of non-operated pts (p=.004)

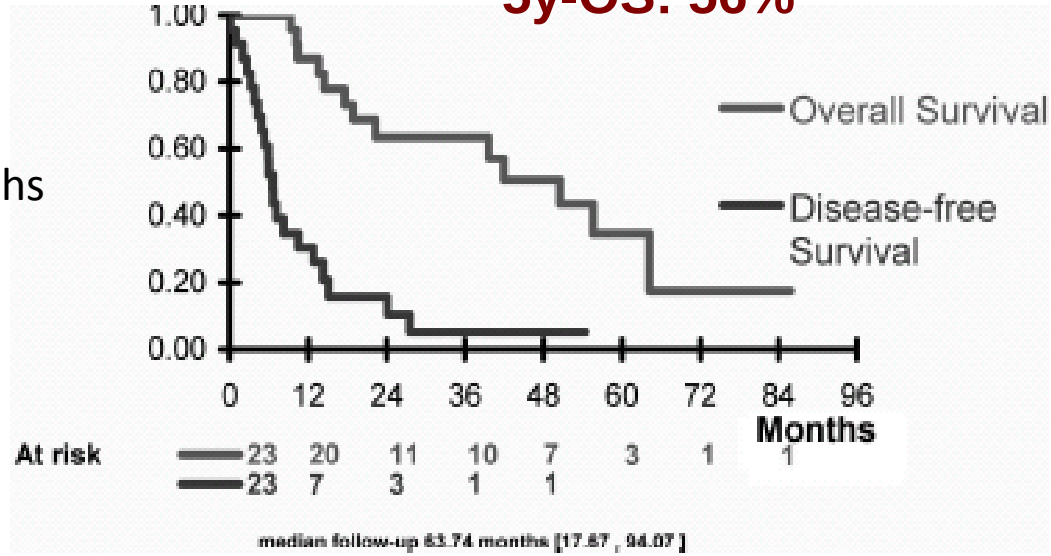
Goéré et al, Ann Surg 2010

3y-OS: 73%

5y-OS: 56%

Median follow-up: 63 months

Operated pts: median OS, 42 months



HAI oxaliplatin with iv 5-FU offers a second chance to remove initially unresectable CRLM in 24% of patients, even after failure of prior 'modern' systemic CTx. Long-term OS can be obtained with this approach.

Goéré et al, Ann Surg 2010

Palliative HAI

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

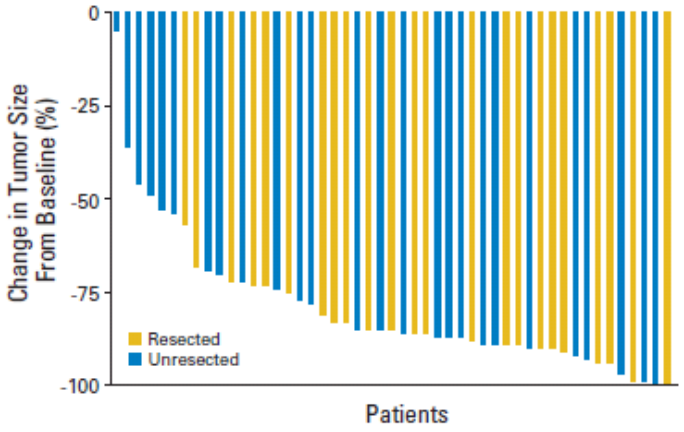
Conversion to Resectability Using Hepatic Artery Infusion Plus Systemic Chemotherapy for the Treatment of Unresectable Liver Metastases From Colorectal Carcinoma

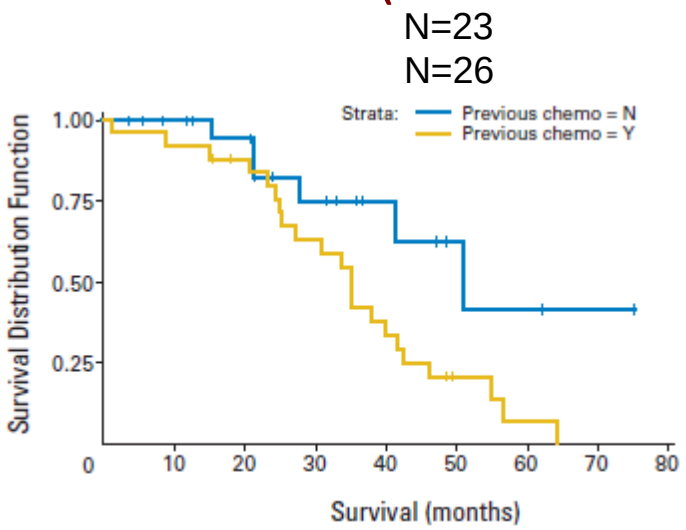
Nancy E. Kemeny, Fidel D. Huitzil Melendez, Marinela Capanu, Philip B. Paty, Yuman Fong, Lawrence H. Schwartz, William R. Jarnagin, Dina Patel, and Michael D'Angelica

Kemeny NE, et al. J Clin Oncol 2009;27:3465-71

Conversion to Resectability Using Hepatic Artery Infusion Plus Systemic Chemotherapy for the Treatment of Unresectable Liver Metastases From Colorectal Carcinoma

- N=49 pts
- Non-resectable CRLM
- HAI FUDR-dexamethasone + IV oxaliplatin-irinotecan
- Conversion to resectability: 23 patients (47%) (R0: 19)
- No predictive factor for resection
- OS increased when HAI performed as 1st line (51 vs 35 months)



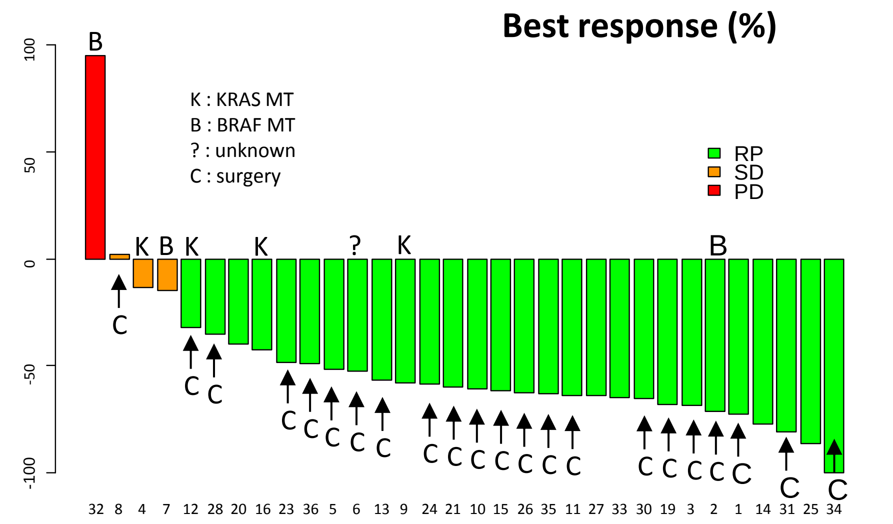


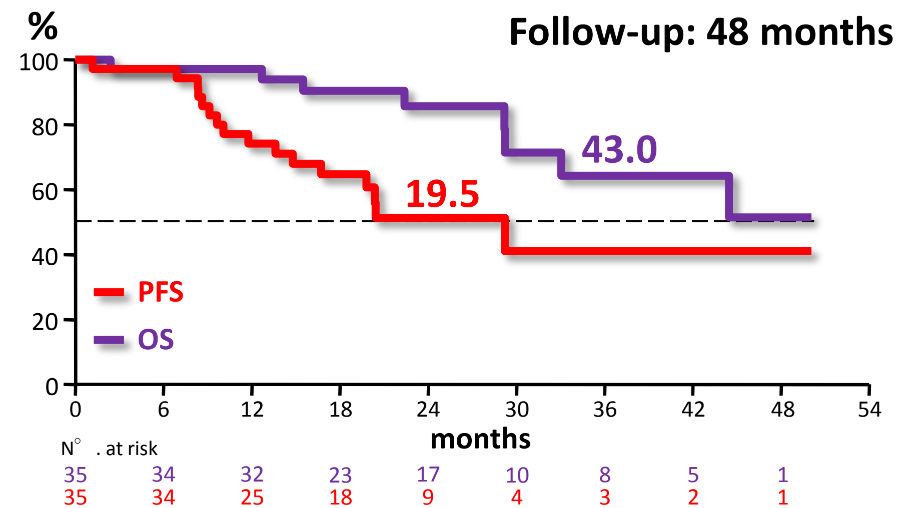
Kemeny et al, J Clin Oncol 2009

Palliative HAI

HAI oxaliplatin + iv LV5FU2-cetuximab 1st line

- **Phase II CHOICE (8 centres)**
- **35 patients, 1st line**
  - → Non-resectable CRLM
  - → *KRAS* WT: 30/35 (86%)
- **ORR: 88% (CR: 3%)**
  - → *KRAS*/BRAF WT: 96%
- **DCR: 97%**
  - → *KRAS*/BRAF WT: 100%
- **Resection: 66% (23/35)**
  - → *KRAS*/BRAF WT: 74%



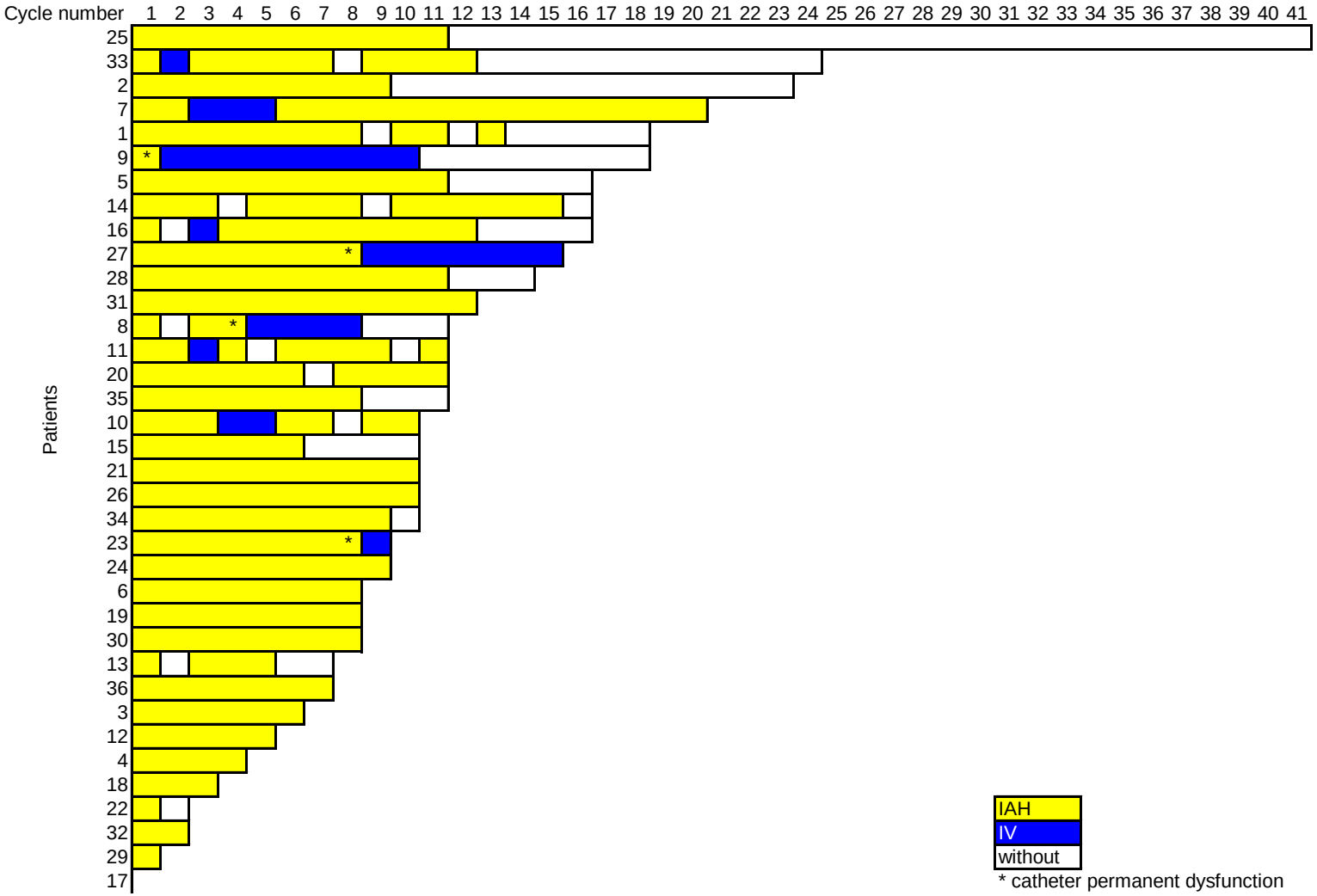


Malka D., *et al.* ESMO 2012

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

Palliative HAI CHOICE Study

(**C**ombined **H**epatic **O**xaliplatin, **I**ntravenous **C**hemotherapy and **E**rbituxTM)



Palliative HAI

HAI oxaliplatin + iv LV5FU2-cetuximab 1st line

17/23 (74%) : non-resectability criteria
- 1 : 7 pts
- 2 : 1 pt
- 3 : 5 pts

Patient	Hepatic involvement								Surgery	Disease progression	Death
	Baseline				Post-treatment						
	LS	HV	PV	IVC	LS	HV	PV	IVC			
1	8	3	1	Yes	5	1	0	-	-		
2	7	2	1	Yes	3	2	0	-	Yes	Yes	
3	3	0	0	-	2	0	0	-	Yes	Yes	-
4	6	2	0	-	5	2	0	-	-	Yes	Yes
5	7	3	2	-	7	1	1	-	Yes	Yes	-
6	3	0	0	-	0	0	0	-	Yes	-	-
7	8	3	2	Yes	8	3	2	Yes	-	Yes	-
8	1	1	1	Yes	1	1	1	Yes	Yes	-	-
9	7	0	1	-	4	0	0	-	Yes	Yes	-
10	7	0	1	-	3	0	0	-	Yes	-	-
11	4	0	0	-	4	0	0	-	Yes	Yes	-
12	4	3	0	-	2	2	0	-	Yes	-	-
13	5	0	1	-	4	0	0	-	Yes	-	-
14	8	3	0	Yes	8	3	0	Yes	-	Yes	Yes
15	8	3	2	Yes	7	2	2	-	-	-	-
16	3	0	1	-	2	0	1	-	Yes	-	-
17	6	1	1	-	2	0	0	-	Yes	-	-
18	8	3	2	Yes	8	1	2	-	-	-	-
19	6	3	2	Yes	2	3	2	Yes	-	-	-
20	7	1	1	-	5	0	0	-	Yes	-	-
21	8	3	2	-	8	1	1	-	-	-	-
22	3	0	0	-	0	0	0	-	-	-	-
23	4	1	0	-	4	0	0	-	Yes	-	-

LS, liver segments. HV, hepatic veins. PV, portal veins. IVC, inferior vena cava.

Conversion of non-resectability criteria: 11/17 (65%)
-1 : 7 pts
-2 : 2 pts
-3 : 3 pts
-4 : 1 pt

Malka D., *et al.* ESMO 2012

Palliative HAI: conclusion

- FUDR, 5FU: modest OS benefit (if any)
- Oxaliplatin: feasibility & tolerance > FUDR
- ‘intensifed’ HAI-IV combos: ORR > 80%, DCR ~100%
- Even after systemic chemotherapy failure
- Conversion to resecability: up to 74% of pts with CRLM

Palliative HAI: indications at Gustave Roussy

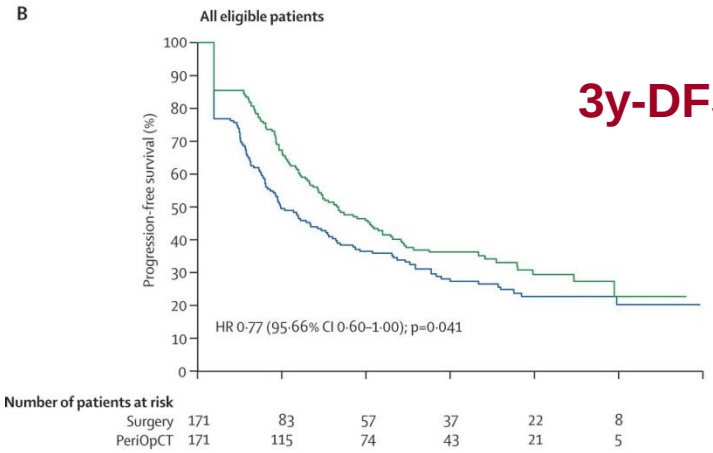
- Non resectable CRLM
- No (or limited) extrahepatic disease
- After systemic chemotherapy failure
- In case of insufficient tumor response, intensification with HAI oxaliplatin in order to convert to resectability
- No underlying liver disease

Adjuvant HAI

- After resection of CRLM
- Liver Recurrence: 30-50%

- Adjuvant CTx with systemic 5 FU

- Perioperative CTx with FOLFOX for pts with ≤ 3 CRLM (EORTC)



3y-DFS: 28% vs 36%, p=0.04

Portier et al, J Clin Oncol 2006
Langer et al, Proc Am Soc Clin Oncol 2002
Mitry et al, J Clin Oncol 2008
Nordlinger et al, Lancet 2008

Adjuvant HAI

Hepatic artery adjuvant chemotherapy for patients having resection or ablation of colorectal cancer metastatic to the liver (Review)

Nelson RL, Freels S

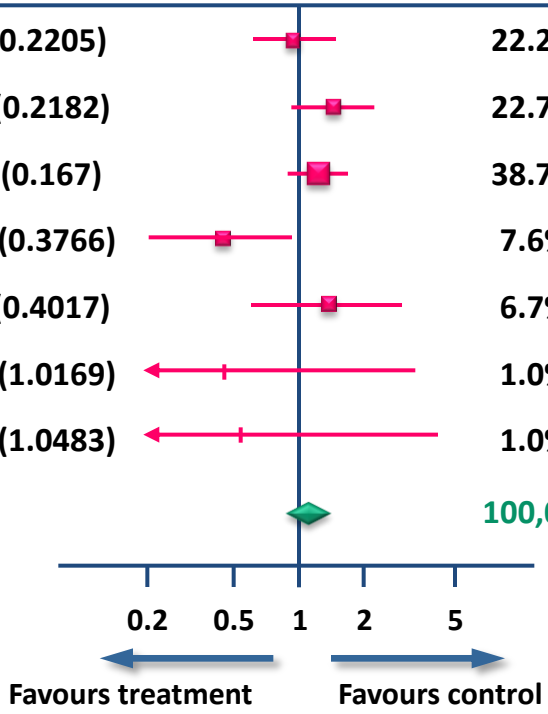
THE COCHRANE COLLABORATION®

Nelson RL, Freels S. Cochrane Database System Rev 2009

Adjuvant HAI

Méta-analysis, Cochrane 2009 (n = 7)

Study or Subgroup	Hepatic Artery Chemo N	Control N	Log [Hazard Ratio] (SE)	Hazard Ratio IV, Fixed, 95% CI	Weight	Hazard Ratio IV, Fixed, 95% CI
Kemeny 1999	74	82	-0.051 (0.2205)		22.2%	0.95 [0.62, 1.46]
Kemeny 2002	53	56	0.3382 (0.2182)		22.7%	1.40 [0.91, 2.15]
Lorenz 1998	113	113	0.1988 (0.167)		38.7%	1.22 [0.88, 1.69]
Lygidakis 1995	20	20	-0.8059 (0.3766)		7.6%	0.45 [0.21, 0.93]
Rudroff 1999	14	16	0.2885 (0.4017)		6.7%	1.33 [0.61, 2.93]
Tono 2000	9	10	-0.8004 (1.0169)		1.0%	0.45 [0.06, 3.30]
Wagram 1990	6	5	-0.6293 (1.0483)		1.0%	0.53 [0.07, 4.16]
Total (95% CI)					100,0%	1.09 [0.89, 1.34]



Hererogeneity: $Chi^2 = 9.27$, df = 6 (P = 0.16); $I^2 = 35\%$
Test for overall effect: Z = 0.83 (P = 0.41)

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

Nelson RL, Freels S. Cochrane Database System Rev 2009

Adjuvant HAI

Méta-analysis, Cochrane 2009 (n=7)

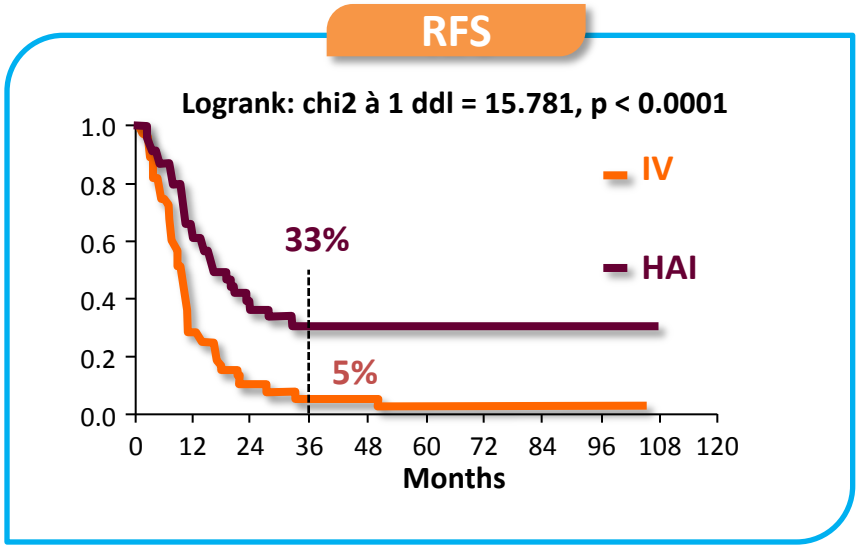
Auteurs	N	CIAH	CT contrôle	SSR hépatique	SSR	OS
Wagman 1990	91	FUDR	-	-	p = 0.03	NS
Lygidakis 1995	40	Carboplatine, 5FU, MMC, IFN	-	p < 0.001	p ≤ 0.001	11 vs 2 mois P ≤ 0.001
Lorenz 1998	226	5FU (+ 5FU IV)	-	21.6 vs 24.0 mois NS	14.2 vs 13.7 mois NS	34.5 vs 40.8 mois NS
Kemeny N 1999	156	FUDR (+ 5FU IV)	5FU IV	90% vs 60% à 2 ans p < 0.001	57% vs 42% à 2 ans p = 0.07	86% vs 72% à 2 ans 72.2 vs 62.2 mois p = 0.03
Tono 2000	19	5FU	-	-	78% vs 30% à 2 ans p = 0.045	78% vs 50% à 5 ans NS
Rudroff 1999	42	5FU + MMC	-	-	15% vs 23% à 5 ans NS	25% vs 31% à 5 ans NS
Kemeny M 2002	75	FUDR (+ 5FU IV)	-	67% vs 43% à 4 ans p = 0.03	46% vs 25% à 4 ans p = 0.04	64 vs 49 mois NS

Adjuvant HAI

HAI oxaliplatin

- **IGR prospective database (2000-09)**
- **98 patients**
  - ➔ OR/SD after preop CTx
  - ➔ **≥ 4** resected CRLM
  - ➔ ≥ 1 adjuvant CTx cycle
- **Treatment**
  - ➔ HAI oxaliplatin, n = 44
  - ➔ IV FOLFOX or FOLFIRI, n = 54
- **Median follow-up: 45 months**

	Multivariate analysis	
	HR	P
HAI vs IV	0.37 [0.23-0.60]	<0.0001
R0 resection	0.47 [0.29-0.76]	0.002



Goéré D.,*et al.* Ann Surg 2013

Adjuvant HAI: PACHA-01

Postoperative hepatic Arterial Chemotherapy in High-risk patients as Adjuvant treatment after resection of colorectal liver metastases

Sponsor: Gustave Roussy - PI: D Goéré - Co-PI : D Malka

Multicenter, randomised Phase 2-3 trial (PHRC 2013)

Isolated CRLM (except ≤ 3 resectable lung nodules)
≥ 4 operated CRLM
- Resection/ablation
- R0 (« potentially » if RFA)

Preoperative CTx
- Oxaliplatin and/or irinotecan
- ± anti-EGFR/antiangiogenic
- ORR or SD

OMS 0-1
≥ 18 yrs
Stratification
- Preop oxaliplatin (O/N)
- Preop CTx duration (≤ 3 vs > 3 m)
- Response to preop CTx (OR vs SD)
- Nb of treated CRLM (4-8 vs >8)
- Centre

R

n = 114

iv mFOLFOX6

Start ≤ 8 weeks postoperatively
Duration: ≥ 3 m; maximum: 6 m
Targeted therapy: allowed if received preop

HAI oxaliplatin + iv LV5FU2

Endpoints
- Primary: 18-month hepatic RFS (30% → 50%)
  - Phase 3
    - 3-yr RFS (15% → 30%; HR : 0,63)
    - 220 patients (+106)
- Secondary: feasibility (≥ 4 cycles), tolerance, RFS, OS

Hepatic Arterial Infusion of chemotherapy (HAI)

Radioembolisation (RE)

TransArterial ChemoEmbolisation (TACE)

RE

JOURNAL OF CLINICAL ONCOLOGY

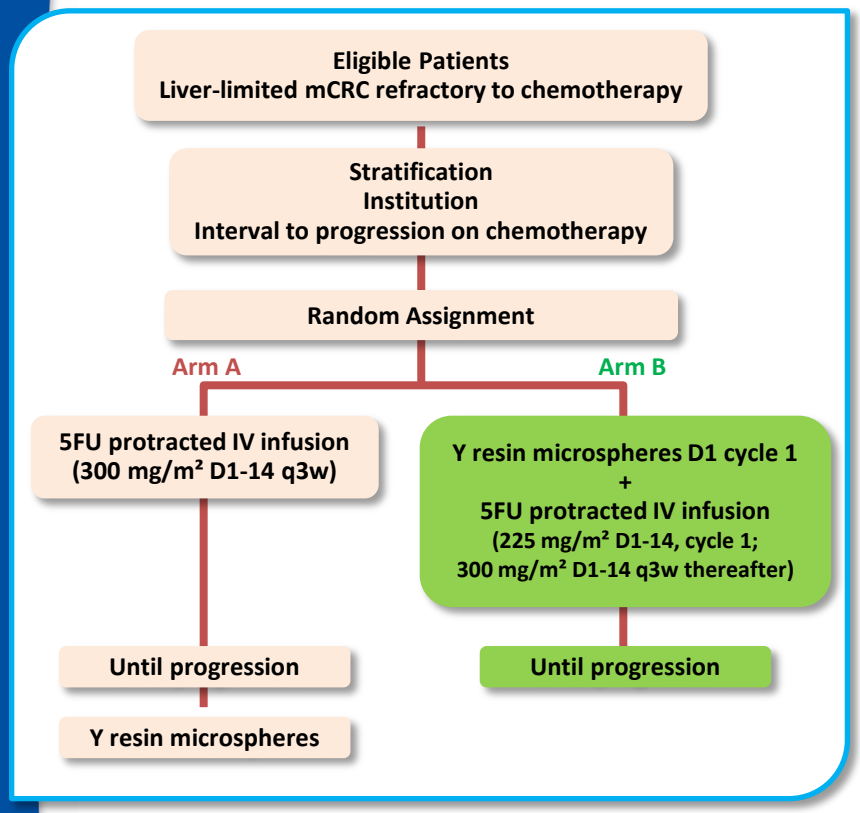
ORIGINAL REPORT

Phase III Trial Comparing Protracted Intravenous Fluorouracil Infusion Alone or With Yttrium-90 Resin Microspheres Radioembolization for Liver-Limited Metastatic Colorectal Cancer Refractory to Standard Chemotherapy

Alain Hendlisz, Marc Van den Eynde, Marc Peeters, Geert Maleux, Bieke Lambert, Jaarke Vannoote, Katrien De Keukeleire, Chris Verslype, Luc Defreyne, Eric Van Cutsem, Philippe Delatte, Thierry Delaunoit, Nicola Personeni, Marianne Paesmans, Jean-Luc Van Laethem, and Patrick Flamen

Hendlisz A, et al. J Clin Oncol 2010;28:3687-94

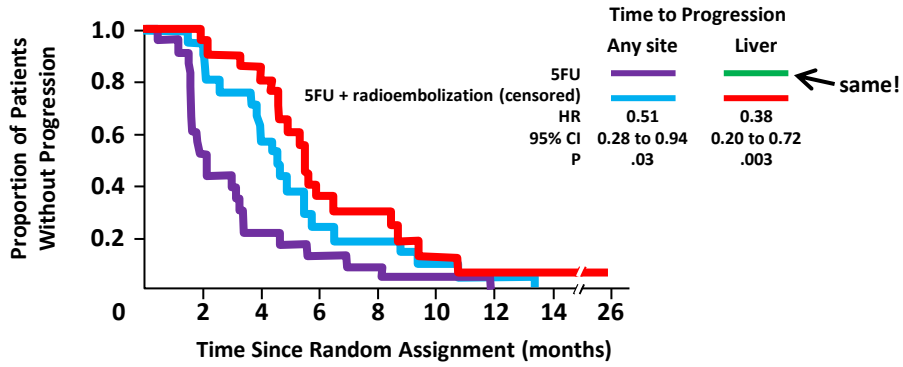
RE



Best Overall Hepatic Response

	FU Alone (n=23)		Radioembolization + FU (n=21)	
Response	**No.**	**%**	**No**	**%**
Partial response	0	0	2	10
Stable disease	8	35	16	76
Progressive disease	14	61	2	10
Nonevaluable	1	4	1	5

NOTE. Comparison of response rates: 0 of 23 versus two of 21, P=.22 (95% CI for the difference between arms B and A ranging from -0.10 to 0.32). Comparison of stabilization rates: eight of 23 versus 18 of 21, P=.001 (95% CI for the difference ranging from 0.19 to 0.71).



Time to Liver Progression, Time to Progression Overall, and Overall Survival

Time to Progression and OS	FU Alone (n=23)	Radioembolization + FU (n=21)	Hazard Ratio	95% CI	P
TTLP, median, months					
All progressions considered as events	2.1	5.5	0.38	0.20 to 0.72	.003
Patients with treatment change censored at the time of change	2.1	5.6	0.35	0.18 to 0.69	.002
TTP, median, months	2.1	4.5	0.51	0.28 to 0.94	.03
OS, median, months	7.3	10.0	0.92	0.47 to 1.78	.80

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

Hendlisz A, et al. J Clin Oncol 2010;28:3687-94

RE

Table 1 Outcomes of Radioembolization with ^{90}Y resin Microspheres for Salvage Therapy of Patients with Hepatic Metastases from Colorectal Cancer

Study	*N*	ORR (%)	SD (%)	Median overall survival (months)
Kennedy et al[22]	208	35.5	54.8	10.5 (responders) 4.5 (nonresponders)
Bester et al[23]	224	NR	NR	11.9
Cosimelli et al[21]	50	24.0	24.0	12.6
Nace et al[26]	51	12.9	64.5	10.2
Cianni et al[24]	41	46.3	36.2	11.6
Jakobs et al[25]	41	17.1	61.0	10.5

Abbreviations: NR, not reported; ORR, objective response rate (complete response plus partial response); SD, stable disease.

Wang DS, et al. Semin Intervent Radiol 2013;30:12–20

RE

Table 1 | Planned or ongoing clinical trials of radioembolization in patients with mCRC

Clinical trial	Study phase	Estimated number of patients	Treatment regimen*	Setting	Primary end points	Duration or projected duration of recruitment
SIRFLOX trial	II–III	318	FOLFOX6m ± ^{90}Y resin microspheres	First line	Progression-free survival	August 2006–December 2011
FOXFIRE trial	II–III	490	OxMdG ± ^{90}Y resin microspheres	First line	Overall survival‡	May 2009–April 2012
FAST trial	II	30	FOLFOX6m + ^{90}Y resin microspheres + bevacizumab (from third cycle)	First line	Adverse effects, safety	July 2008–December 2011
University of California San Diego trial	II	34	^{90}Y resin microspheres	Before second line	Progression-free survival	To be confirmed
Goshen Health System trial	II	20	^{90}Y resin microspheres + FOLFOX, FOLFIRI or floxuridine	First or second line	Tumor response, adverse effects	November 2005–June 2009
M. D. Anderson Cancer Center trial	II	60	Irinotecan + cetuximab ± ^{90}Y resin microspheres	Second or third line	Progression-free survival	October 2008–October 2010
Jules Bordet Institute salvage trial	II	56	5-FU ± ^{90}Y resin microspheres	Salvage§	Time to liver progression	January 2005–December 2008
Capecitabine dose-escalation trial (FCCC)	I–II	37	Capecitabine + ^{90}Y resin microspheres	Not specified¶	Adverse effects, safety, maximum tolerated dose	June 2006–June 2009
Robert H. Lurie Cancer Center trial	I	30	Capecitabine + ^{90}Y glass microspheres	Third line‖	Adverse effects, maximum tolerated dose, time to progression	February 2009–July 2010
Southwestern Regional Medical Center trial	I–II	50	^{90}Y glass microspheres	Not specified‖	Tumor response rate, adverse effects, survival time	December 2006–December 2008
MDS Nordion trial	II	150	^{90}Y glass microspheres	Not specified§,#	Liver progression-free survival	January 2007–January 2013
SITILO salvage trial	II	50	^{90}Y resin microspheres	Salvage§	Tumor response rate	May 2005–August 2008
End-stage matched control study	II	58	^{90}Y resin microspheres vs best supportive care	Salvage§	Overall survival	October 2005–July 2008

*For chemotherapy regimens refer to Table 2. ‡Combined prospective statistical analysis with SIRFLOX study. §Eligible patients have chemotherapy-refractory disease. ‖Eligible patients have primary or metastatic liver tumors. ¶Eligible patients for the dose-escalation cohorts can have primary or metastatic liver tumors; eligibility for the phase II cohort is restricted to mCRC. #Eligible patients have mCRC or non-CRC liver metastases. Abbreviations: 5-FU, 5-fluorouracil; FCCC, Fox Chase Cancer Center; mCRC, metastatic colorectal cancer; OxMdG, oxaliplatin, 5-FU and leucovorin followed by 5-FU.

Nicolay NH, et al. Nat Rev Clin Oncol 2009;6:687-97

RE

Table 3 | Adverse event profile associated with radioembolization treatment

Adverse event	Incidence (%)	Timing of adverse events associated with radioembolization	Prevention or treatment of adverse event
Fever	>50	Onset on day of radioembolization, duration up to 1 week	No treatment necessary
Abdominal pain	~50 (~10 grade III and/or IV)	Onset during radioembolization, duration up to 24 h	Analgesia during and for several days after radioembolization
Nausea	~40 (<5 grade III and/or IV)	Onset during radioembolization, duration up to 24 h	Antiemetic medication before and after radioembolization
Fatigue	~40 (<5 grade III and/or IV)	Onset within 1 month of radioembolization, duration up to 2 weeks	Adequate hydration and nutrition, oral corticosteroids may be considered
Lymphopenia	~50 (<10 grade III and/or IV)	Onset within 14 days of radioembolization, duration up to 3 months	No treatment necessary
Abnormal LFT results	~20–40 (~1–6 grade III and/or IV)	Transient abnormalities, especially in combination with chemotherapy or in patients with cirrhosis	No treatment necessary
Radiation gastritis	~5–10 (~1–2 grade III and/or IV)	Onset during or after radioembolization as a result of nontarget delivery of microspheres	Careful microsphere application, pretreatment embolization of extrahepatic vessels, prophylactic proton pump inhibitors for 1–2 months after treatment
Radiation-induced liver disease	<5	Onset 1–3 months after radioembolization, possibility of ascites, permanently elevated LFT values, liver fibrosis*	Careful dosimetry, careful microsphere application, possible dose reduction in patients with reduced hepatic reserve
Radiation pancreatitis	<1	Onset during or after radioembolization as a result of nontarget delivery of microspheres	Careful microsphere application, pretreatment embolization of extrahepatic vessels
Radiation cholecystitis	<1	Onset during or after radioembolization as a result of nontarget delivery of microspheres	Careful microsphere application, pretreatment embolization of extrahepatic vessels, cholecystectomy may be necessary
Radiation pneumonitis	No reported cases since implementation of pretreatment ^{99m}Tc lung shunt	NA	Pretreatment ^{99m}Tc lung shunt with macroaggregated albumin, careful dosimetry with lung doses <30 Gy

*Patients should undergo clinical review 1, 2, 3 and 4 months after radioembolization to check for radiation-related sequelae that may require medical or surgical intervention. Abbreviation: LFT, liver function test.

Nicolay NH, et al. Nat Rev Clin Oncol 2009;6:687-97

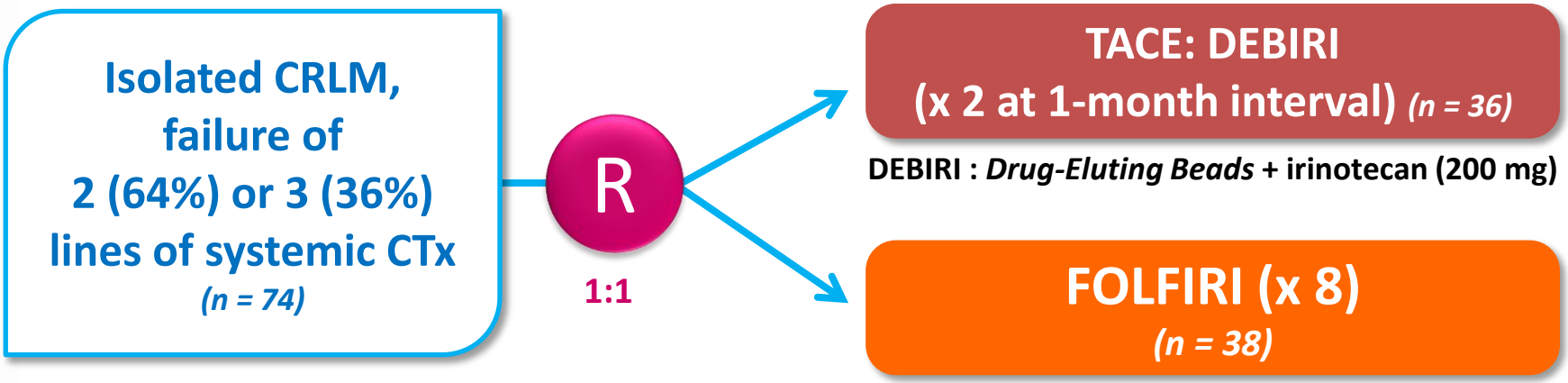
Hepatic Arterial Infusion of chemotherapy (HAI)

Radioembolisation (RE)

TransArterial ChemoEmbolisation (TACE)

TACE

Italian Phase III

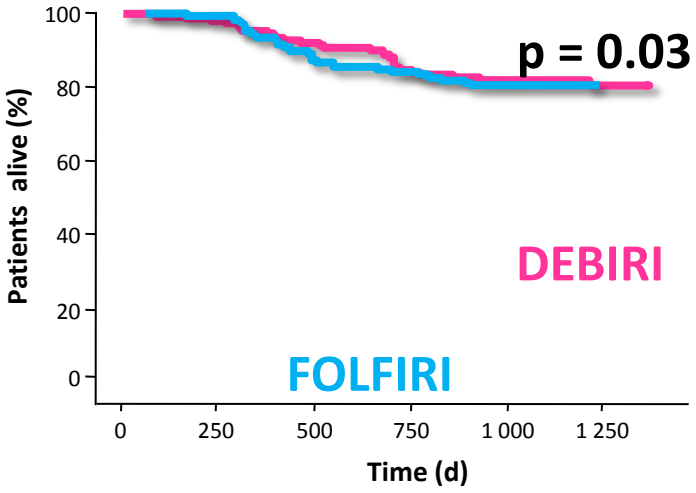


- **Primary objective: increase 2-yr OS by 40% (HR: 0.72)**

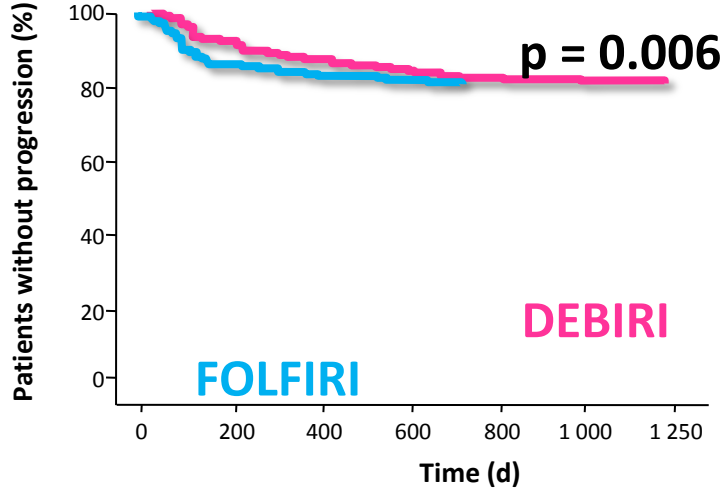
Fiorentini G, et al. ASCO GI 2012;abstr. 587

TACE

OS



PFS



	OS	*ORR*	PFS	Toxicity		Increase in QOL*	Cost
				Early (G2/3)	Late (G2)		
DEBIRI (n = 34)	**22 m**	***69%***	**7 m**	**70%****	**20%**	**60%**	**5000 € (2 Deb)**
FOLFIRI (n = 35)	**15 m**	***20%***	**4 m**	**25%**	**80%**	**22%**	**18000 € (8 CTx)**

Median follow-up: 50 months (range: 26-64)
** Edmonton score compared to baseline*
*** pain, vomiting, fatigue*

Fiorentini G.,*et al.* ASCO GI 2012;abstr. 587

Stereotactic Body Radiation Therapy (SBRT)

SBRT

Table 1 Streotactic body radiotherapy for oligo-recurrence within nodal area in colorectal cancer

Ref.	Study year	No. of patients	Proportion of oligo-nodal metastases	SBRTdose (Gy)[1]; range (median)	Outcomes		
					LC	OS	Severe GI toxicity
Bae *et al*[69]	2012	41	44%	45-60 (48)	57% (5 yr)	38% (5 yr)	7%
Kang *et al*[68]	2010	59	53%	36-51 (42)	24% (5 yr)	29% (5 yr)	3%
Kim *et al*[55]	2009	7	100%	36-51 (48)	(-)	71% (3 yr)	14%
Kim *et al*[75]	2008	23	100%	30-51 (39)	74% (4 yr)	25% (4 yr)	4%
Hoyer *et al*[66]	2006	64	5%	45 (45)	63% (2 yr)	38% (2 yr)	5%

[1]Three fractions of streotactic body radiotherapy were used in all studies. LC: Local control; OS: Overall survival; GI: Gastrointestinal.

SBRT

Stereotactic Body Radiotherapy for Colorectal Liver Metastases

A Pooled Analysis

Daniel T. Chang, MD[1]; Anand Swaminath, MD[2]; Margaret Kozak, BA[1]; Julie Weintraub, MD[3]; Albert C. Koong, MD, PhD[1]; John Kim, MD[2]; Rob Dinniwell, MD[2]; James Brierley, MD[2]; Brian D. Kavanagh, MD, MPh[3]; Laura A. Dawson, MD[2]; and Tracey E. Schefter, MD[3]

Cancer September 1, 2011

SBRT

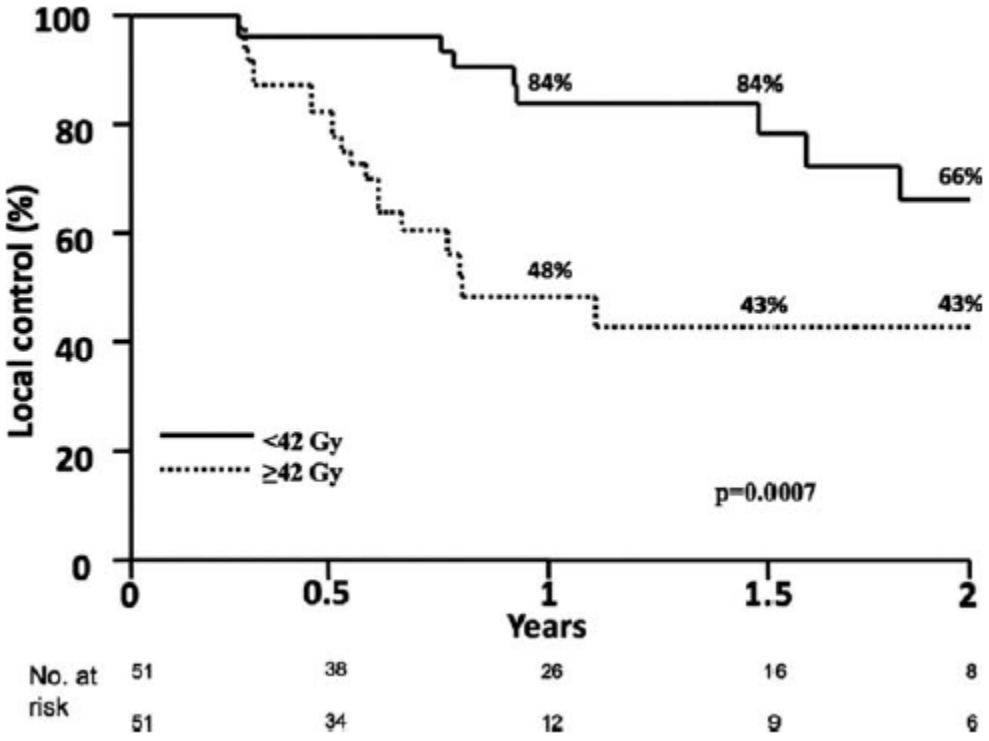
Stereotactic Body Radiotherapy for Colorectal Liver Metastases

A Pooled Analysis

Daniel T. Chang, MD[1]; Anand Swaminath, MD[2]; Margaret Kozak, BA[1]; Julie Weintraub, MD[3]; Albert C. Koong, MD, PhD[1]; John Kim, MD[2]; Rob Dinniwell, MD[2]; James Brierley, MD[2]; Brian D. Kavanagh, MD, MPh[3]; Laura A. Dawson, MD[2]; and Tracey E. Schefter, MD[3]

Cancer September 1, 2011

SBRT


100
80
60
40
20
0
Local control (%)
84%
84%
66%
48%
43%
43%
<42 Gy
≥42 Gy
p=0.0007
0
0.5
1
1.5
2
Years
No. at risk
51
38
26
16
8
51
34
12
9
6

Conclusion

- HAI catheters vs HAI CTx
  - ➔ HAI KT: easy for surgeons, learning curve for interventional radiologists
  - ➔ HAI CTx: more demanding than systemic CTx
- HAI oxaliplatin
  - ➔ Better tolerated, more convenient and at least as effective than FUDR
  - ➔ A peculiar and frequent AE: pain during infusion
  - ➔ Adjuvant setting: ↗ RFS, to be confirmed by a randomized trial
  - ➔ Palliative setting:
    - ▶ Highly effective in oxaliplatin-naïve pts (FNLCC, CHOICE)
    - ▶ Effective in 2nd line and beyond, even after failure of oxaliplatin-based systemic CTx
- RE, TACE, SBRT
  - ➔ Effective in 2nd line and further
  - ➔ 1st line?
  - ➔ + systemic CTx?