

Feasibility of Neoadjuvant Drug-Eluting Bead Irinotecan (DEBIRI) for Resectable Colorectal Liver Metastases

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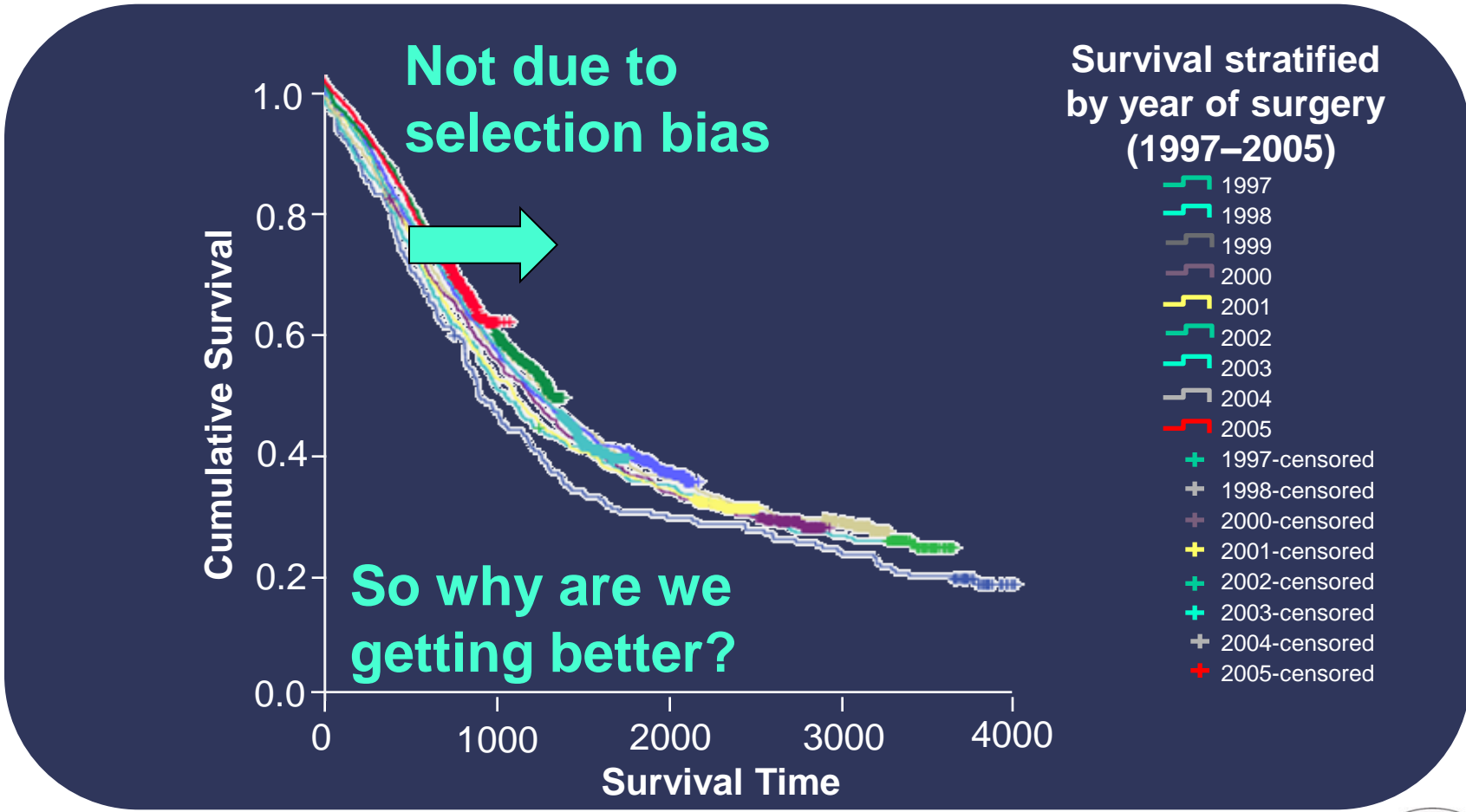


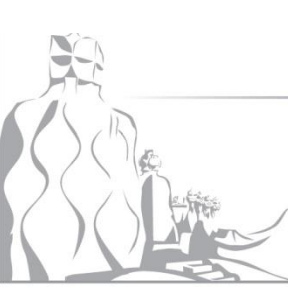
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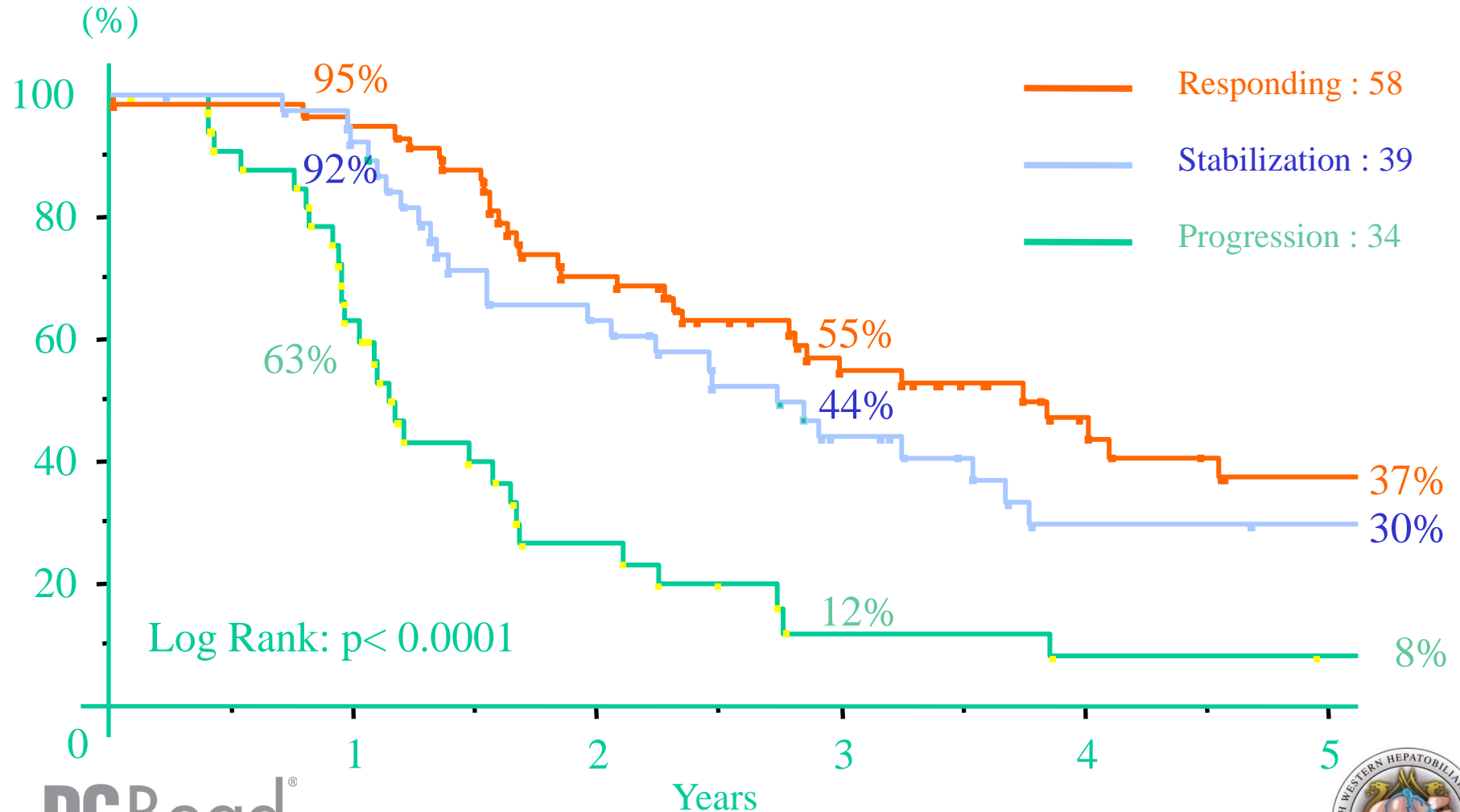


Survival After Liver Resection for Colorectal Liver Metastases (England 1997-2005)



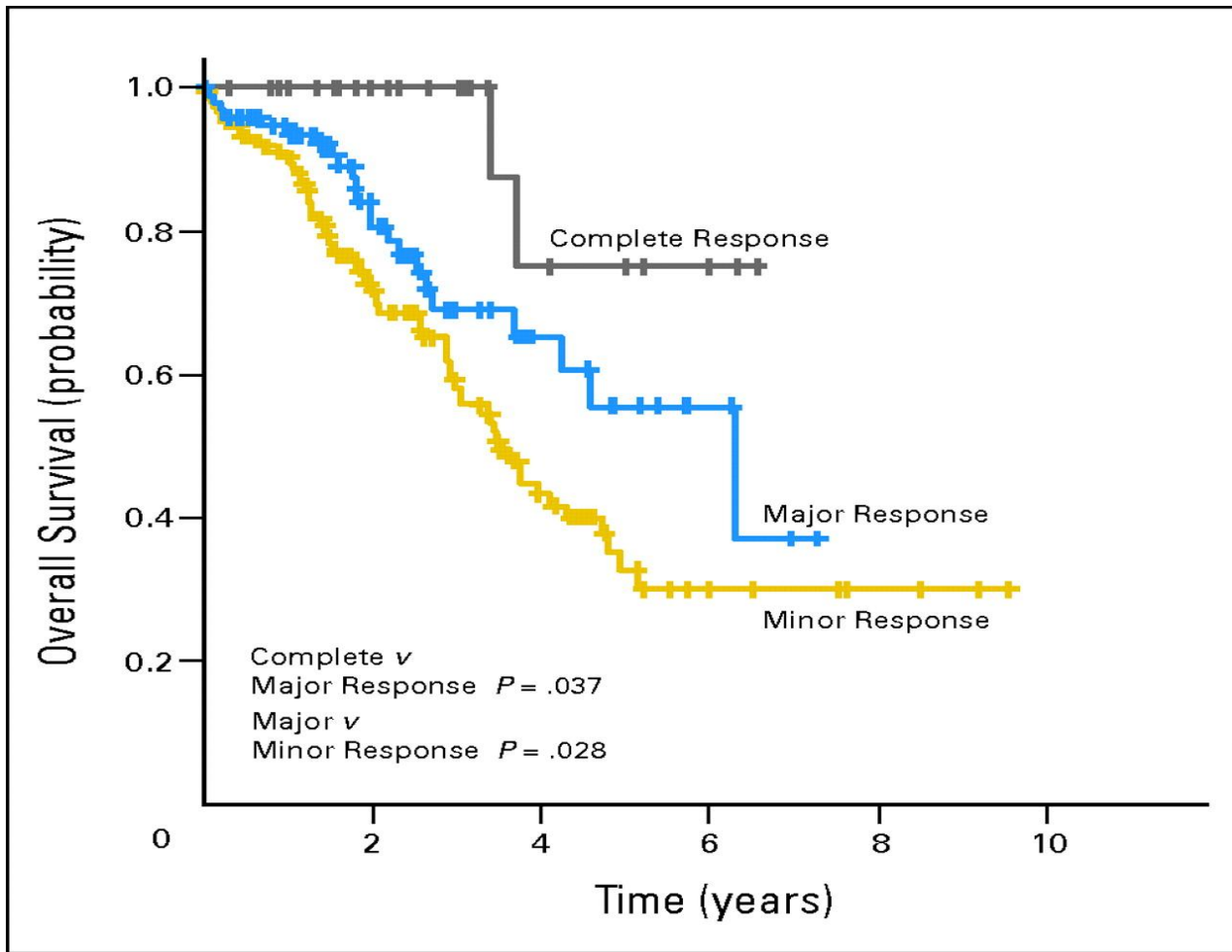
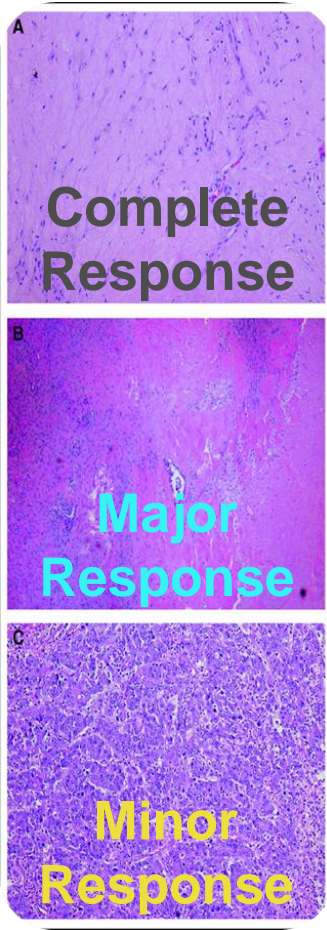


Overall survival after resection of multiple liver metastases according to chemotherapy response



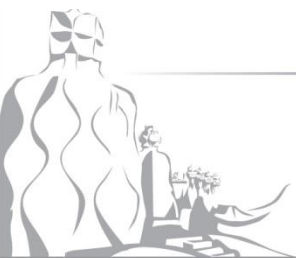


Correlation of Outcome After Hepatectomy to Histologic Response to Neoadjuvant Chemotherapy



Blazer et al. JOURNAL OF CLINICAL ONCOLOGY 2008; 26: 5344-51



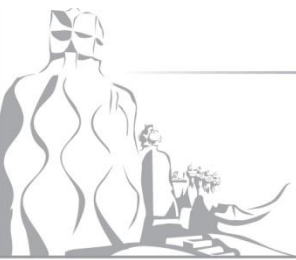


Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial

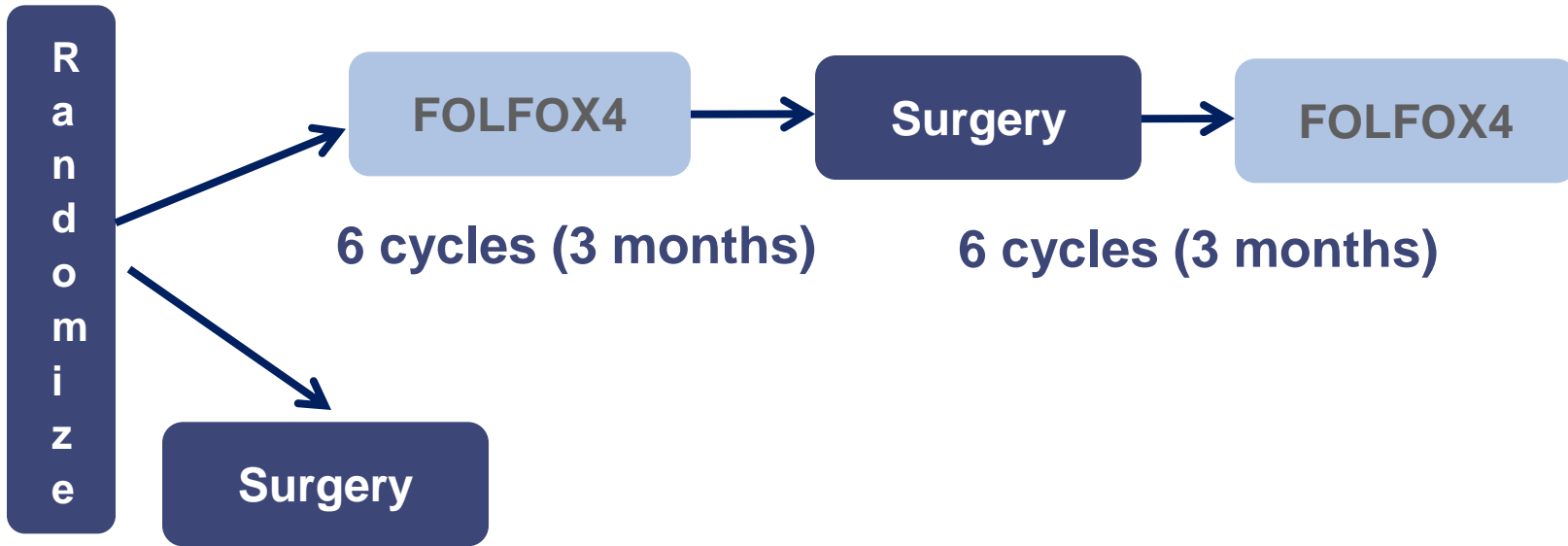
Bernard Nordlinger, Halfdan Sorbye, Bengt Glimelius, Graeme J Poston, Peter M Schlag, Philippe Rougier, Wolf O Bechstein, John N Primrose, Evan T Walpole, Meg Finch-Jones, Daniel Jaeck, Darius Mirza, Rowan W Parks, Laurence Collette, Michel Praet, Ullrich Bethge, Eric Van Cutsem, Werner Scheithauer, Thomas Gruenberger for the EORTC Gastro-Intestinal Tract Cancer Group, * Cancer Research UK, * Arbeitsgruppe Lebermetastasen und-tumoren in der Chirurgischen Arbeitsgemeinschaft Onkologie (ALM-CAO), * Australasian Gastro-Intestinal Trials Group (AGITG), * and Fédération Francophone de Cancérologie Digestive (FFCD)*

Lancet 2008; 371: 1007-1016



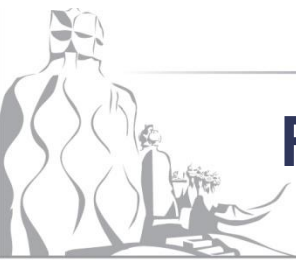


Study Design



n=364 patients

Nordlinger et al. Lancet 2008; 371: 1007-16

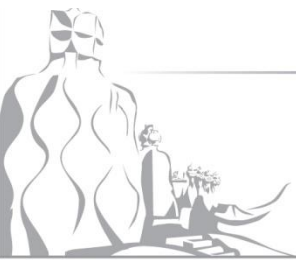


RECIST Response After Pre-operative CT

Nordlinger et al. Lancet 2008; 371: 1007-16

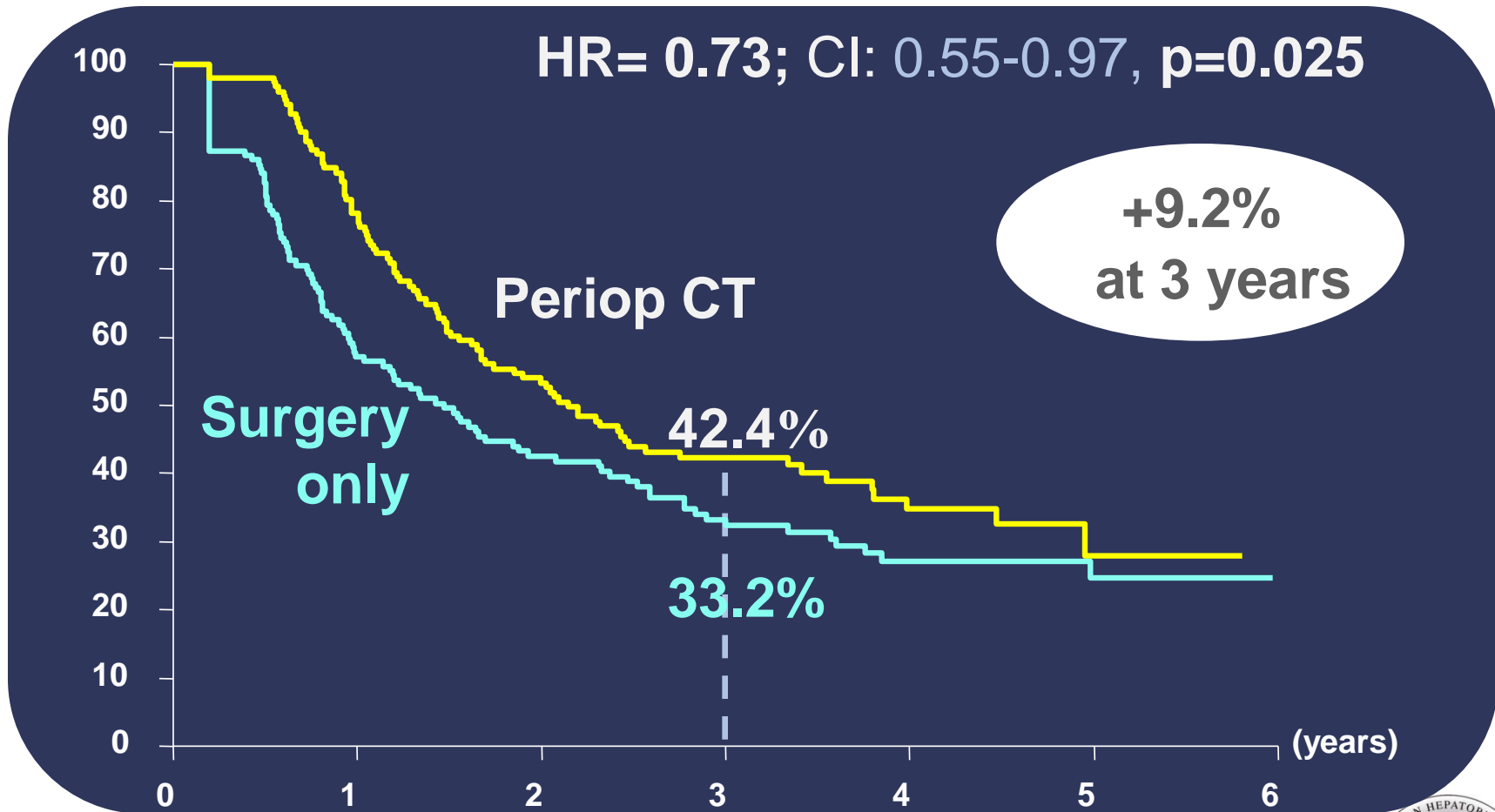
- **Complete response:** 7 (3.8%)
- **Partial response:** 73 (40.1%)
- **Stable disease:** 64 (35.2%)
- **Progressive disease:** 12 (6.6%)
 - 8 progressed after 3-4 cycles, 3 were resected
 - 4 progressed after 6 cycles, 1 was resected
- **Not evaluable** 26 (14.3%)
- **Ineligible** 7
- **Benign lesion** 3
- **<3 cycles** 12
- **No follow-up measures** 4

Total: 182 patients



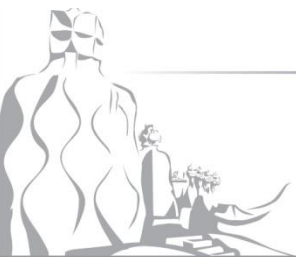
Progression-Free Survival in Resected Patients

Nordlinger et al. *Lancet* 2008; 371: 1007-16



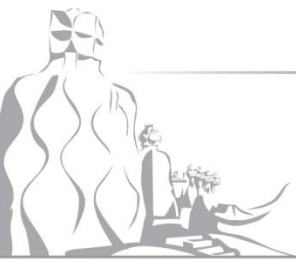
O	N	Number of patients at risk					
104	152	85	59	39	24	10	
93	151	118	76	45	23	6	



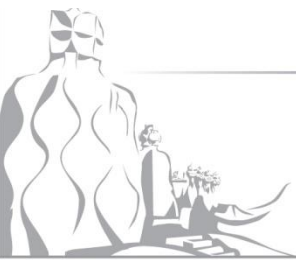


Complications of Surgery

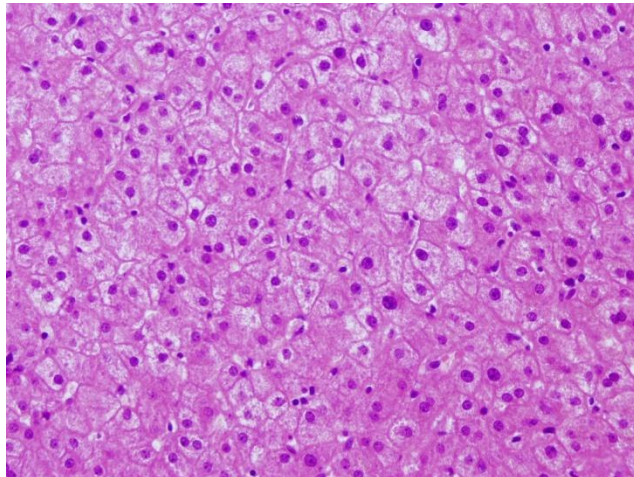
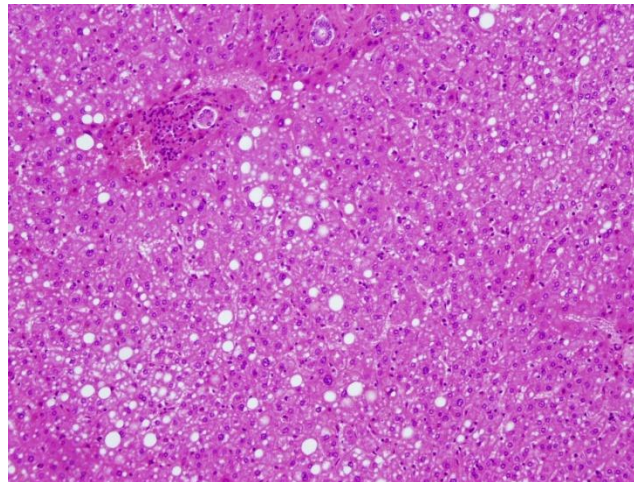
	Peri-op CT	Surgery
Post-operative complications*	40/159 (25.2%)	27/170 (15.9%)
Cardio-pulmonary failure	3	2
Bleeding	3	3
Biliary Fistula <i>(Incl Output >100ml/d, >10d)</i>	12 (9)	5 (2)
Hepatic Failure <i>(Incl Bilirubin >10mg/dl, >3d)</i>	11 (10)	8 (5)
Wound infection	4	4
Intra-abdominal infection	8	2
Need for reoperation	5	3
Other	25	16
Incl. post-operative death	1 patient	2 patients



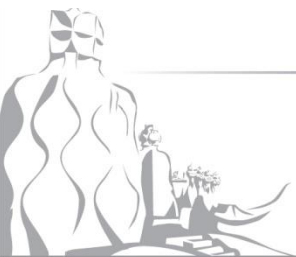
Problems with Preoperative Chemotherapy in Liver Surgery



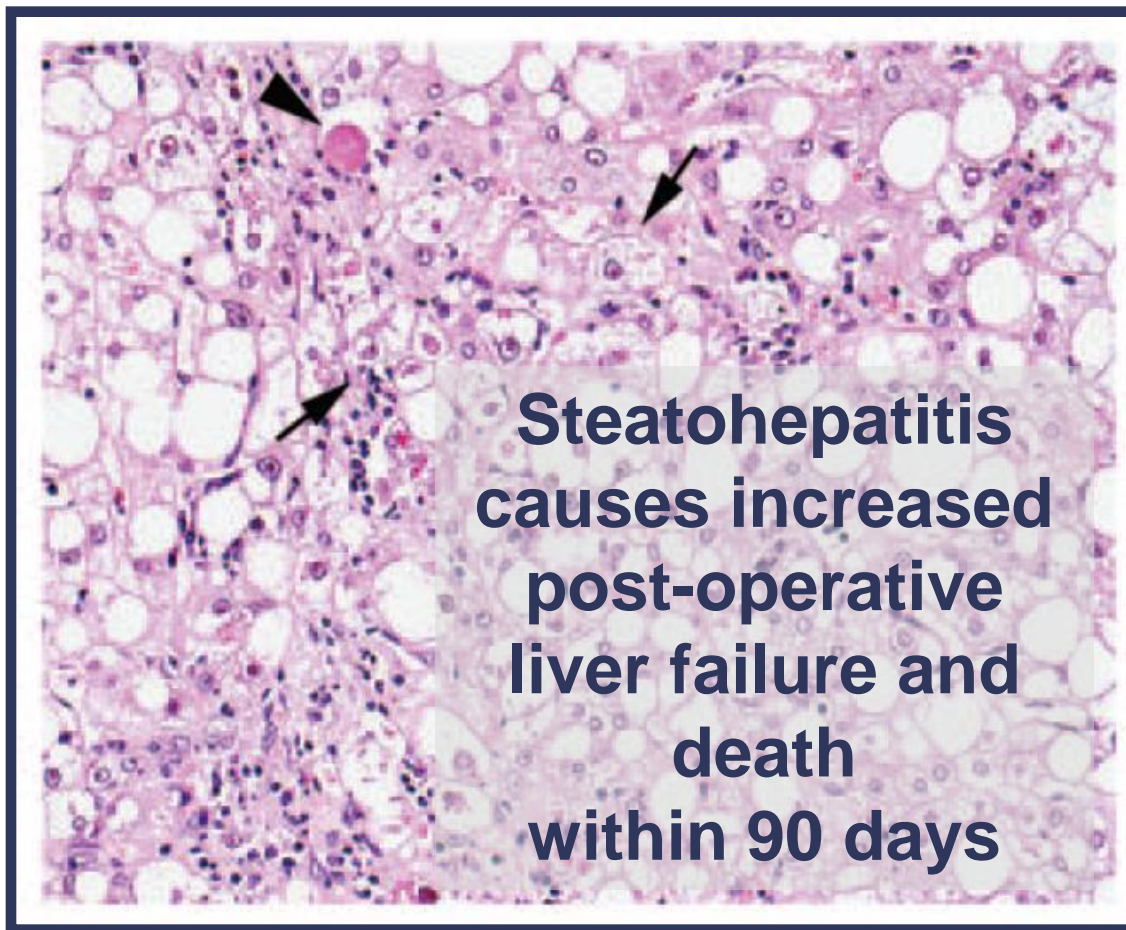
Liver After Prolonged Chemotherapy (Not Observed After <6 Cycles)



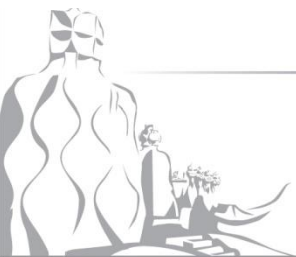
**We used to call this
'chemotherapy associated
steato-hepatosis'
(CASH)**



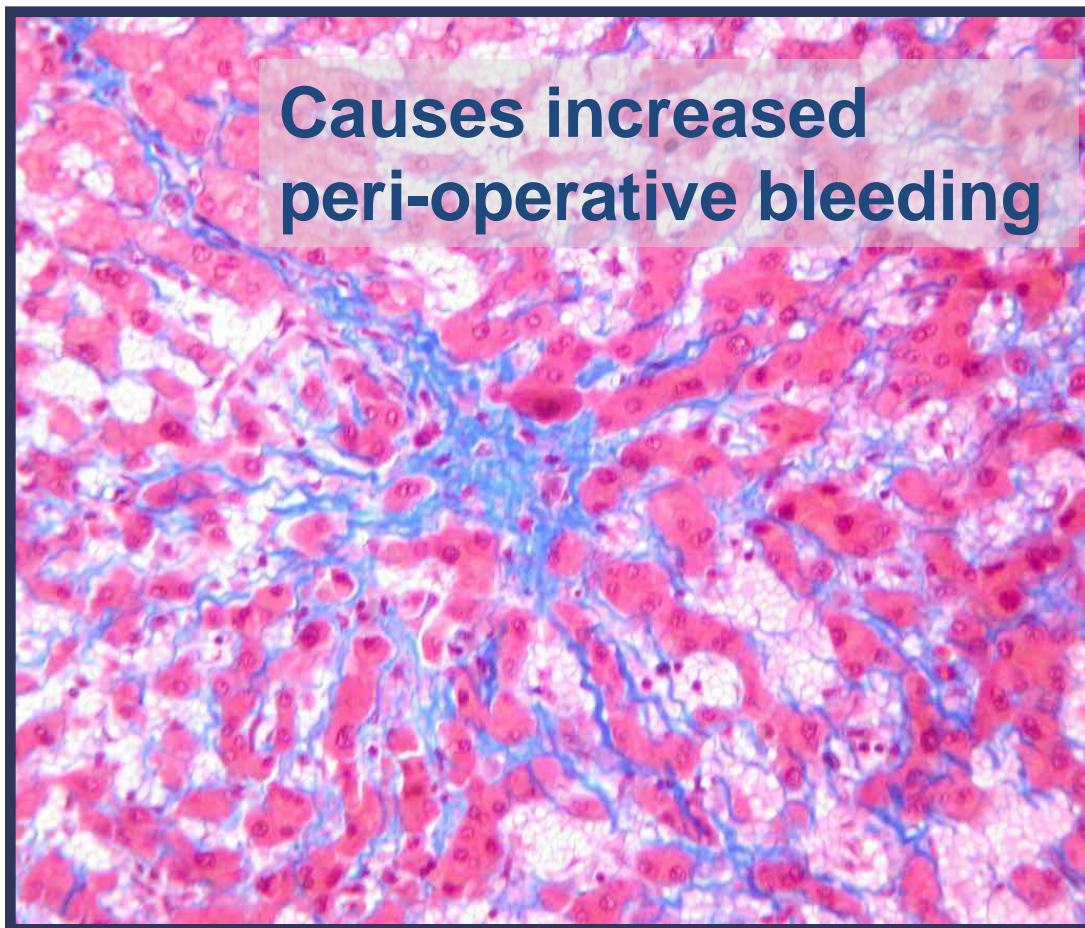
Steatosis and Steatohepatitis: Seen with Irinotecan



Vauthey J-N, et al. *J Clin Oncol* 2006; 24: 2065–2072.



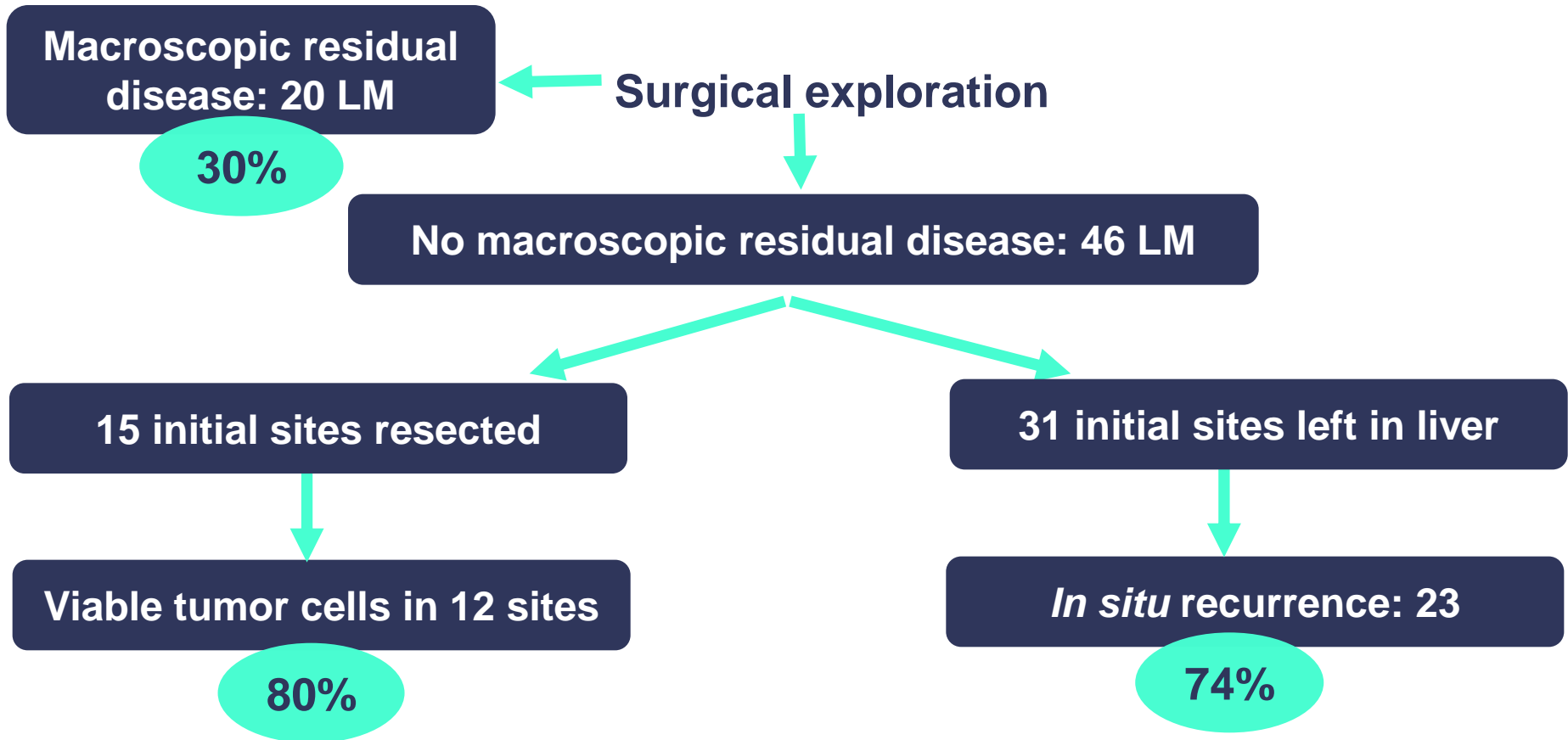
Sinusoidal Obstruction Syndrome: Seen with Oxaliplatin but not Irinotecan





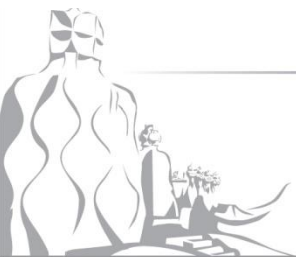
CT- Based Evaluation

66 metastases disappeared on imaging after CT

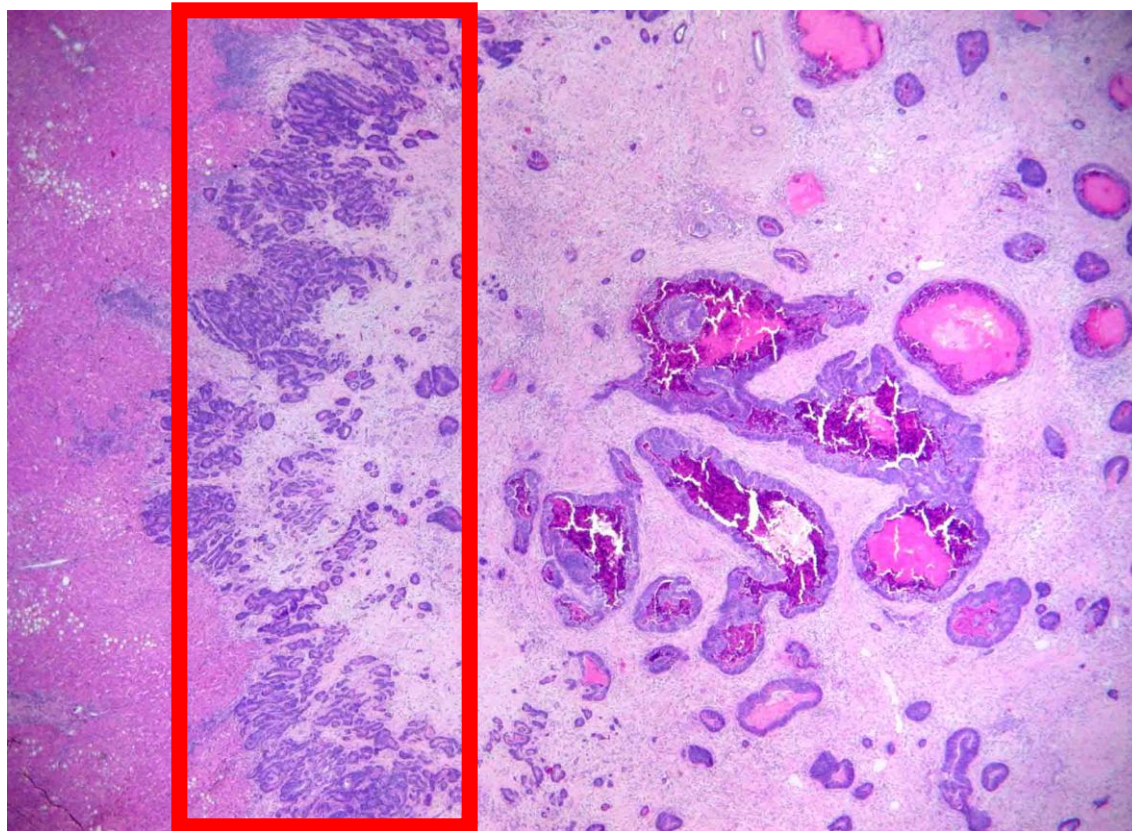


55/66 (83%) LM non-cured

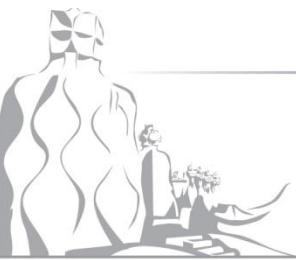
Benoist et al. JCO 2006;24:3939-45



Macroscopic CR After Chemotherapy: ~20% of Cells in Periphery are Viable



Courtesy of Professor Gilles Mentha, University of Geneva



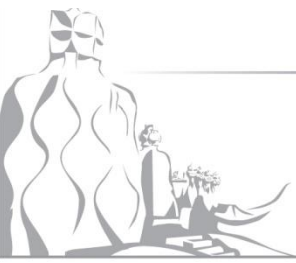
Too Much Pre-Surgery Chemotherapy

- *The liver surgeon's nightmare*
- **Excessive oxaliplatin causes sinusoidal congestion and thrombosis:**
 - excessive bleeding at surgery
- **Excessive irinotecan causes steatosis and steatohepatitis:**
 - increased risk of post-operative liver failure and 90-day death
- **Disappearing tumours!**



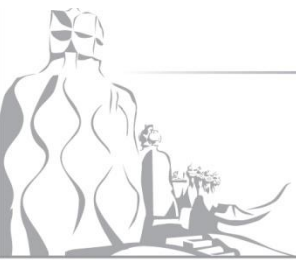
Targeted Chemotherapy?

Treatment	Response Rate	Secondary Resection Rate	Survival
Irinotecan DC Bead TACE	?	?	?



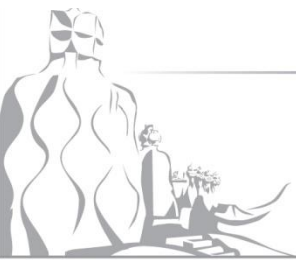
What Would be the Putative Advantages of DC Bead TACE Over Triplet or Doublet+Biologic Therapy?

- **Single administration, so reduced hepatic and systemic toxicity?**
- **Targeted, so protecting 'normal' liver?**
- **Could be combined with metal filings to radio-locate disappearing lesions?**
- **Cheaper?**
- **Faster action, so possibly shorter delay from treatment to surgery?**



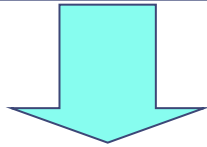
Trial Design

- **Phase II study to evaluate safety/toxicity of targeted neoadjuvant irinotecan carrying DC beads in patients with resectable colorectal liver metastases**
- **Primary end point: tumour resectability (%R0 resections)**
- **Secondary end points:**
 - pathologic response to single treatment
 - radiologic response to single treatment
 - feasibility and operative safety
 - disease free survival at 1, 3 and 5 years

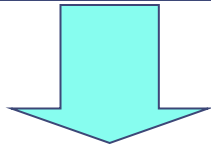


Trial Design

20 patients with easily resectable colorectal liver metastases

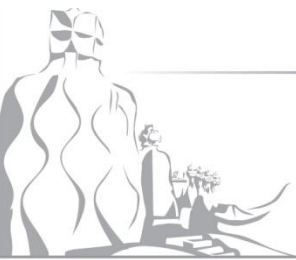


One TACE using DC Bead[®] (Drug-Eluting Bead) irinotecan (DEBIRI)



4 weeks later: liver resection
• Primary endpoints
• Secondary endpoints

- **Standardise centrally:**
 - Radiology
 - Histopathology
- **Sites to recruit:**
 - Liverpool (Aintree)
 - Basingstoke
 - Paris (Villejuif)
 - Gerona
- **Competitive studies:**
 - UK: New EPOC
 - EORTC: BOS



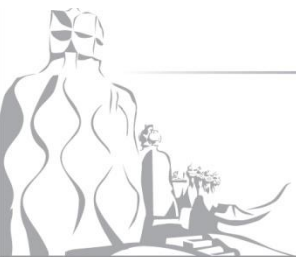
Study Opened January 2009

- **Four centres:**
 - Liverpool
 - Basingstoke
 - Villejuif
 - Gerona
- **19/20 patients recruited to date**
- **19 successful embolisations**
- **All 17 operated: one 30-day post-operative death due to pseudomembranous colitis (non-treatment related)**



Poston et al. ASCO 2010 Abstract 3560

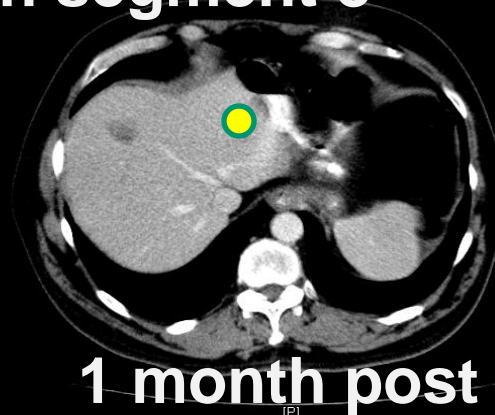
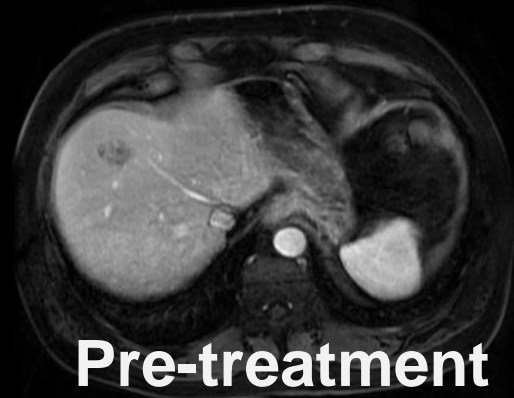




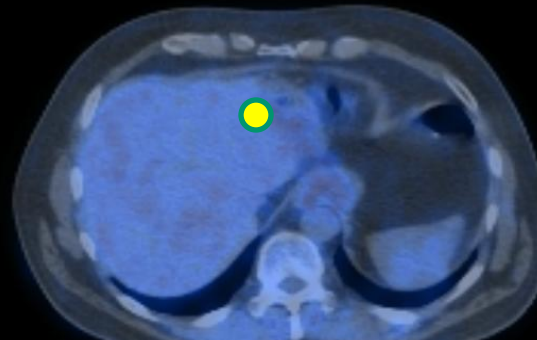
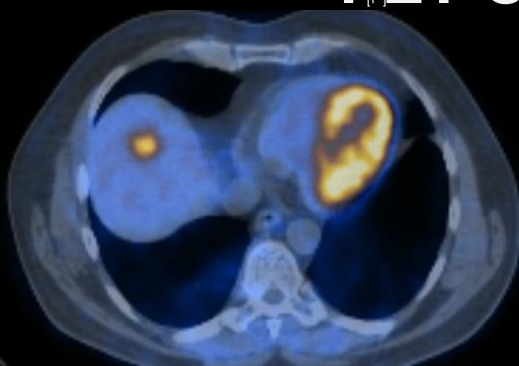
Radiology of Case 6

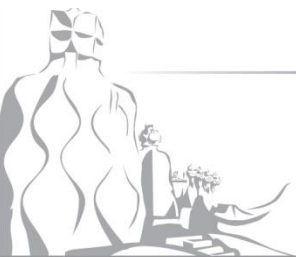
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Known lesion segment 8



PET-CT pre-treatment



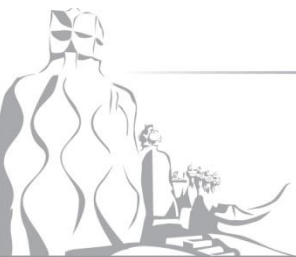


Irinotecan Bead Tumour Embolisation

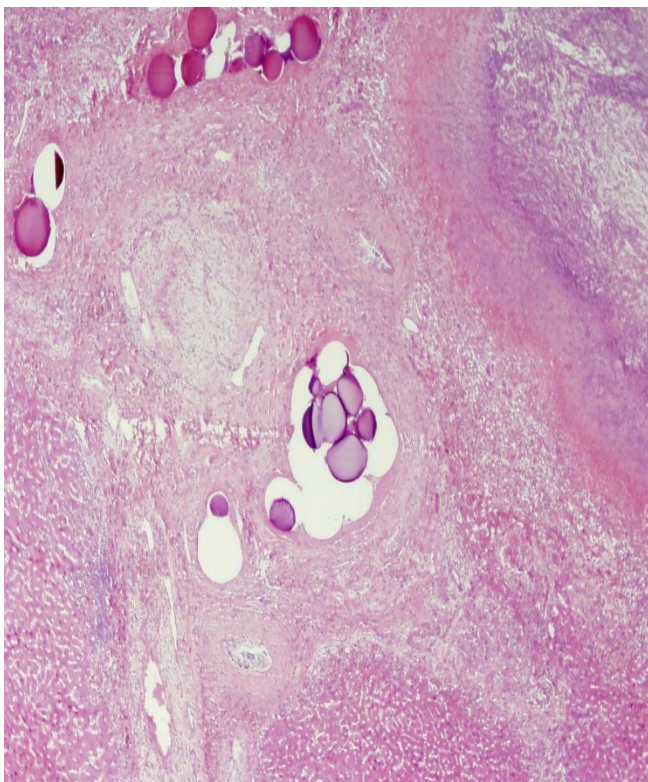


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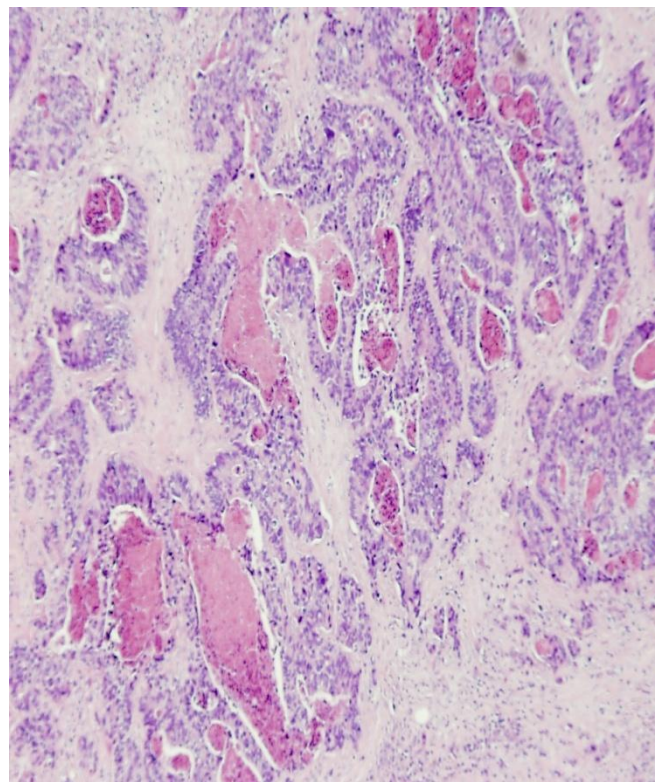




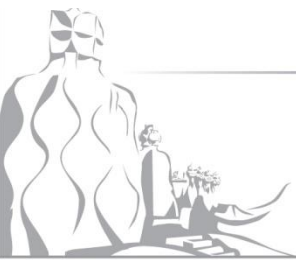
Result of Embolisation



Treated metastasis

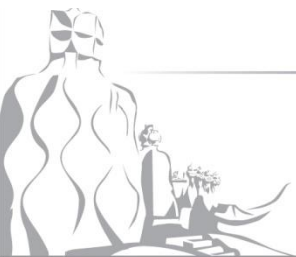


Untreated metastasis

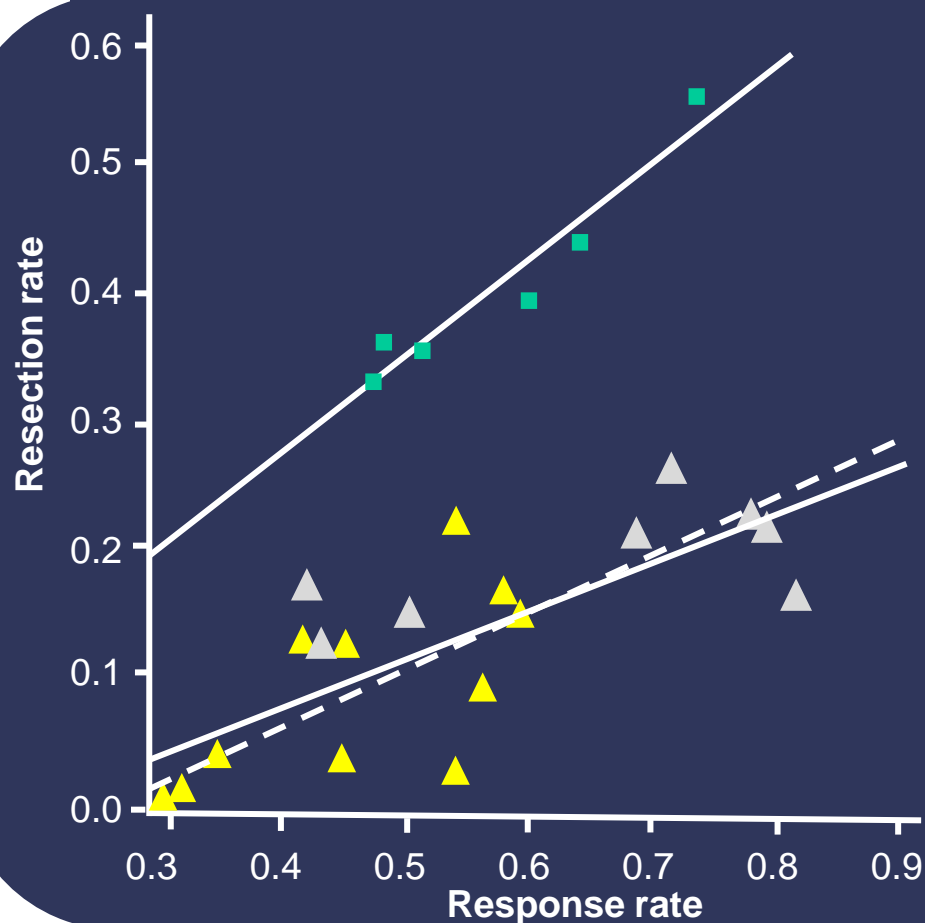


Outcomes

- **19 patients recruited and embolised**
- **17 now operated**
- **One unrelated postoperative 30 day death (pseudomembranous colitis)**
- **No other significant morbidity**
- **50% demonstrate 90-100% tumor necrosis**
- **30% demonstrate 50-90% tumor necrosis**
- **20% demonstrate <50% tumor necrosis**



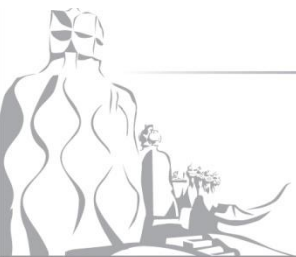
Resection Rate of Metastases and Tumour Response



Studies including selected patients
(liver metastases only, no extrahepatic disease)
($r=0.96$; $p=0.002$)

Studies including non-selected patients with mCRC (solid line)
($r=0.74$; $p<0.001$)

Phase III studies including non-selected patients with mCRC (dashed line)
($r=0.67$; $p=0.024$)

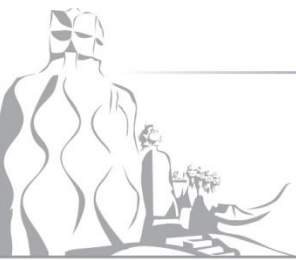


Hepatic arterial infusion (HAI) FOLFOX + ERBITUX

- Phase II study: 1st-line HAI oxaliplatin + IV 5-FU/FA + ERBITUX in patients with KRAS wt non-resectable liver metastases of CRC
- Preliminary data for patients (n=31) with KRAS wt tumors:

ORR	81%
Disease control rate	87%
R0 resection/RFA	48%
Median PFS*	20 months

*Median follow-up 14 months



Subsequent Studies in CRLM?

- **Randomised Phase III to demonstrate potential benefit in 3 yr DFS between systemic chemotherapy +/- DC-irinotecan bead TACE in the neoadjuvant setting for resectable CRLM**
- **Randomised Phase II/III to compare response between irinotecan DC Bead TACE +/- systemic chemotherapy + biologicals in non-resectable CRLM with primary end point being secondary resection**



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