Colorectal Liver Metastases: What the biologist, the surgeon and the medical oncologist should learn from each other.

Serge EVRARD

- From 1880 to 1980, surgeons have learned to retrieve primary tumors
- Metastases were conceptually excluded from any surgical approach
- After 1980, progresses in chemotherapy opened a tight window to surgical resection, especially for CRLM
- Nowadays, CRLM is the best model of multidisciplinary management of a metastatic disease
- … and other metastatic targets like lung mets or peritoneum are presently addressed

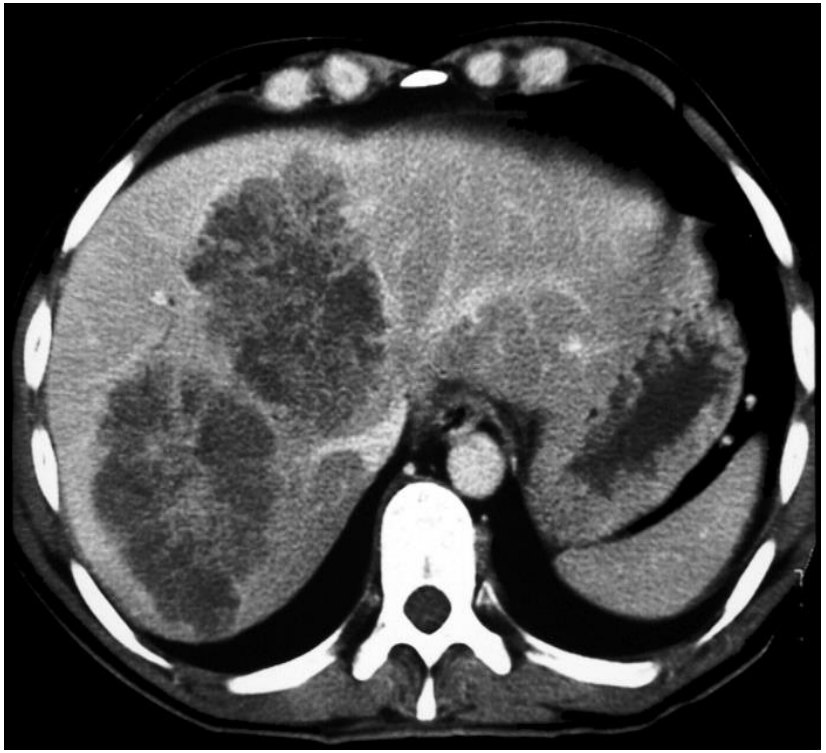
The liver … a fantastic surgical playground!

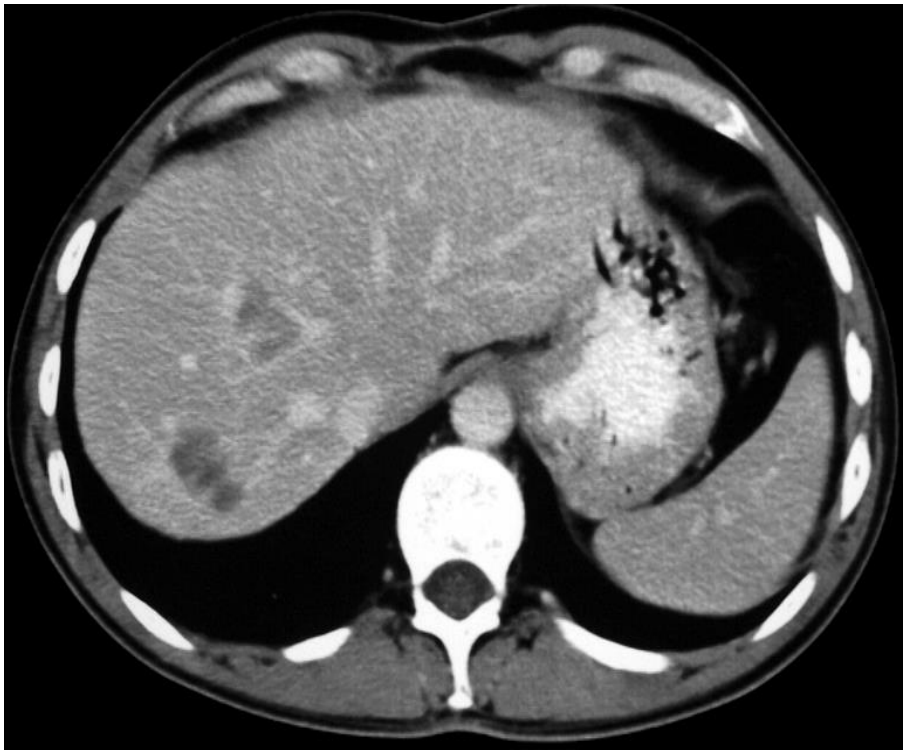
- A lot of techniques
  - Hepatotomies
  - Ablation
  - IOUS
  - Clips, bipolar forceps, stapling, CUSA etc.
  - Hemostatic materials
  - Extra corporeal pump
- A lot of different strategies
  - Anatomical resections
  - Non anatomical resections
  - Extensive hepatectomies versus iterative targeted resections
  - CARe
  - 1, 2 o 3 stage hepatectomies
- Plastic modeling of the liver
  - Get a hypertrophy of the healthy liver and an atrophy of the spread liver to retrieve!

CRLM … as a major playground for chemotherapy

- Several drugs
  - Doublets, triplets
- Several targeted therapies
  - antiVEGF, AntiEGFR
- Several routes of administration
  - Systemic, intra-arterial
- Several strategies
  - Neoadjuvant, conversion , adjuvant, sandwich

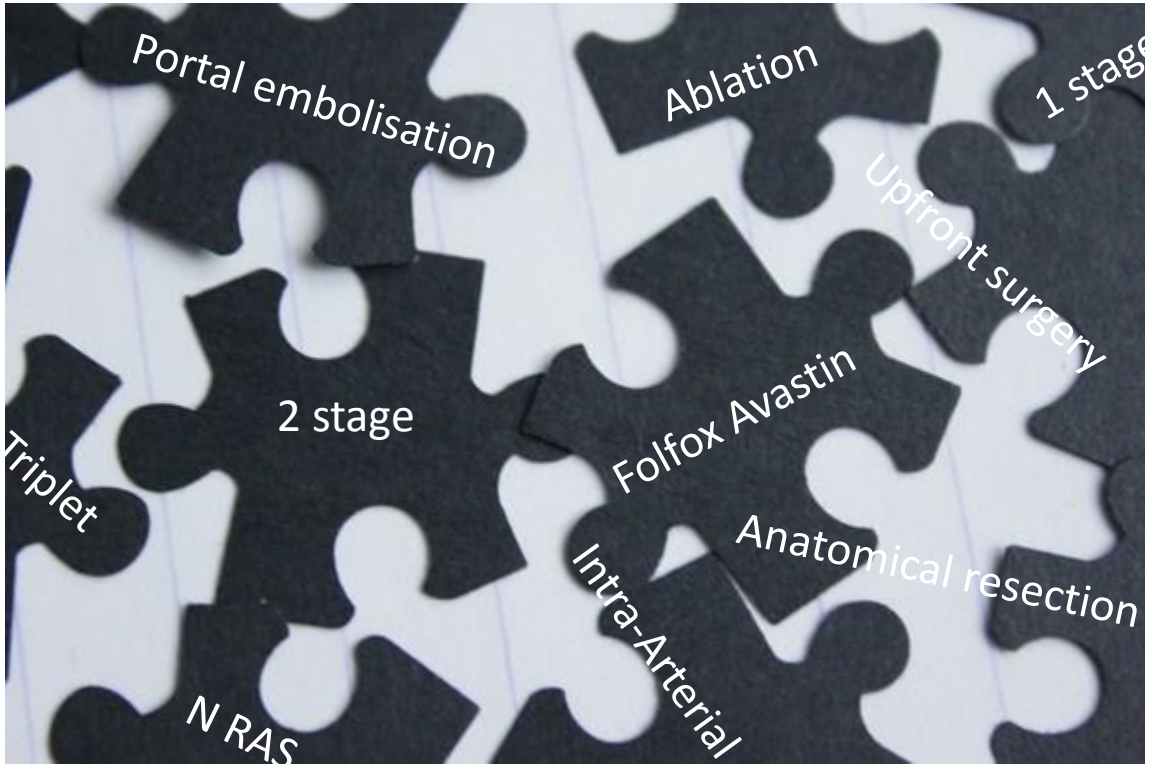
Before …





.. and after chemo !

How will you choose?



Maybe biology could help you?

"Biology is King, selection is Queen, technical maneuvers are the Prince and Princess.
Occasionally the prince and princess try to overthrow the powerful forces of the King and Queen, sometimes with temporary apparent victories, usually to no long term avail."

Blake Cady, MD

Tribute to

George Frederick Hegel

- History tends to follow an assumption of linear progression
- A **dialectical progression** between concepts
- An analogy with Darwin Evolution theory accepted in cell biology
- **Liver Mets surgery also follows a linear progression of its concepts!**

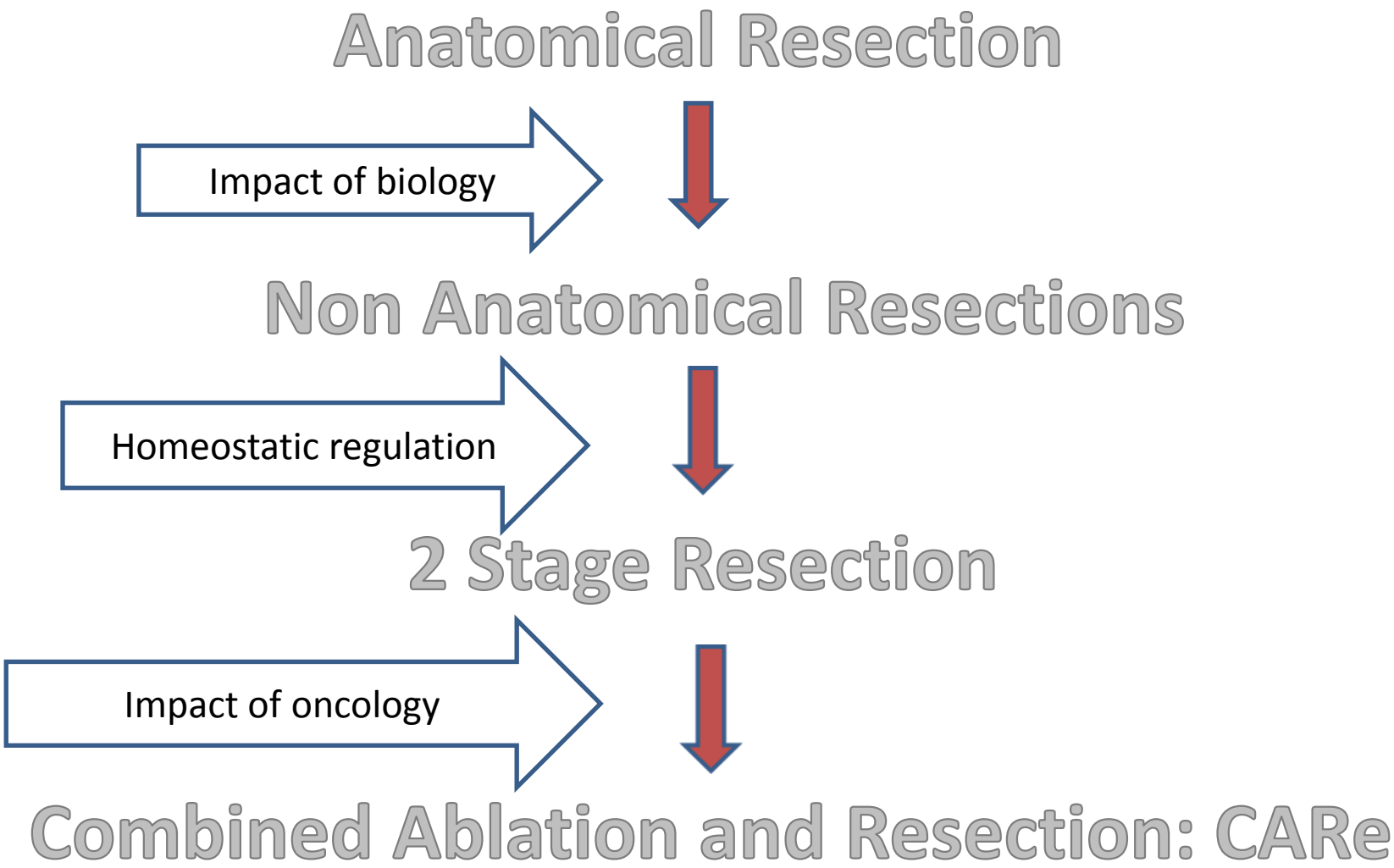
Des maladies biologiques très différentes

- Grand hétérogénéité tumorale
  - Turtoi et al (Hepatology 2014)
- Synchronisme et métachronisme
- Concepts de syndromes oligo et polymétastatiques
  - RAID study: 3-year OS: 30% vs. 60% regarding extra-liver disease.
  - Solitary LM: '*Is perioperative chemotherapy useful for solitary, metachronous, colorectal liver metastases*?' (Adam et al 2010)
  - Genomic characterization of 'Liver only' vs. multi-site (Bruin 2013 Ann Surg Oncol)

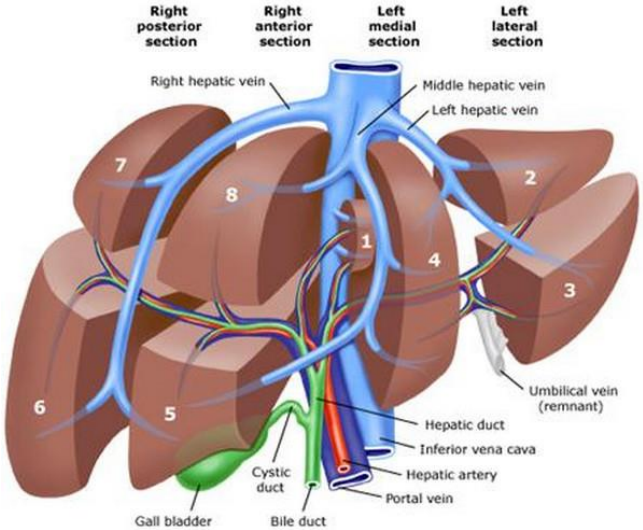
Que doivent savoir les chirurgiens de la biologie?

- **Les micrometastases sont potentiellement partout**: Les resections prophylactiques sont un non-sens! **Le parenchyme normal n'est pas une cible! Les hépatectomies extensives prophylactiques appartiennent au passé de l'oncologie!**
- La sortie de dormance peut être iatrogenique: impact de la qualité des suites sur la survie. Quality improvement program? The ESSO/EORTC *CLIMB* project
- Micrometastases sont souvent métachroniques: Très haut risque de récidive: **La chirurgie doit être conceptualisée sur le mode itératif!**

Evolution of the concepts



Anatomical Resections



- **Couinaud's classification**
- **Impulse of Liver transplant surgery (80ies)**
- The '*never more than 3*' rule
- The '*Anatomical Resection*' rule - easy to apply
- *'Anatomic segmental hepatic resection is superior to wedge resection as an oncologic operation for colorectal liver metastases'*. MSKCC New York (deMatteo et al 2000)

Non Anatomic Resection

- On what basis?
- Clearance margins:
  - 10mm: (Cady et al 1992)
  - 2mm: (Kokudo et al 2002)
  - 0mm: (de Haas et 2008)
- 2715 patients analysed by a propensity score case-match approach: 1 mm cancer-free resection margin achieved in patients with CLM should be considered the standard of care (Hamady et 2013)

8 years later …

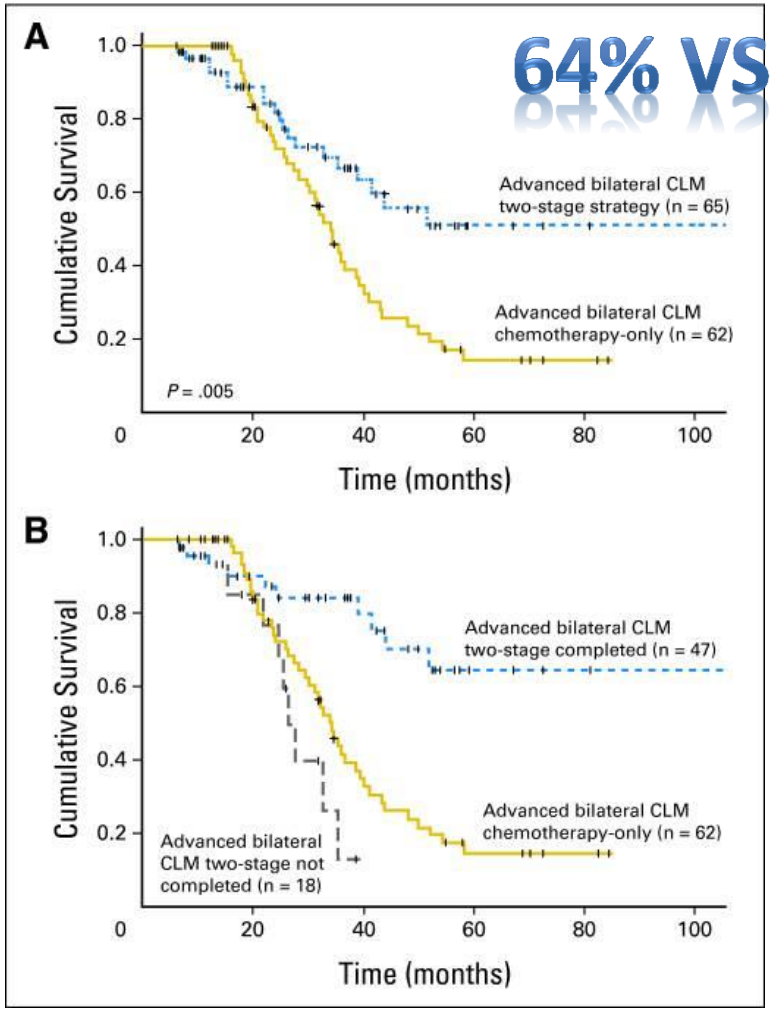
‘Increased Use of Parenchymal-Sparing Surgery for Bilateral Liver Metastases From Colorectal Cancer Is Associated With Improved Mortality Without Change in Oncologic Outcome: Trends in Treatment Over Time in 440 Patients’. MSKCC . (Gold et al 2008)

Next Step:
What is the main limit to resection?
- liver function!

- So, let ‘s expend the normal parenchyma
- Liver homeostasis: No equivalence in surgical oncology. To play with the size of the target
- A fantastic idea: Portal Vein Obliteration
- why not ALPPS?

2-stage

- Avoids liver failure
- Allows to operate more patients
- Excellent results: MD Anderson (Brouquet et al 2011)
  - 51% of 5-year OS (vs. 15% in a retrospective medical group)
  - But 2 groups: the winners and … the losers (25%)!



64% VS 15% 5-YEAR OS

13% VS 42% 3-YEAR OS

2-stage resection

- A fantastic tool in the surgical armamentarium
- But complex, hard to withstand for the patient
- Expensive
- Is it a technique which would allow us to pass in one stage only??

Next step: Intra-operative ablation

- Radiofrequencies or Microvawes
- A non anatomical *in situ* destruction of LM
- **To be skilled in IOUS**
- 1999: Curley et al
- 2000: Elias et al
- 2004: Abdalla et al
- 2006: 'Controversies between surgical and percutaneous radiofrequency ablation' (Evrard et al 2006)

Intra-operative Ablation

- 2012: 2 prospective phase 2 trials
  - CLOCC trial (Ruers et al 2012)
  - ARF2003 (Evrard et al 2012)
- Local recurrences: 4 and 6% (size dependent)
- PFS increased in the CLOCC vs. chemo only
  - 3-year PFS: 27.6% vs. 10.6%
- ARF2003: 5-year OS of 43%
- Low morbi-mortality
- QoL linked to clinical remission

Oncosurgical approach of unresectable colorectal liver metastases: Time to surgical de-escalation?

The *CARe* concept

Evrard Serge, Poston Graeme, Diallo Abou, Brouste Véronique, Lalet Caroline, Desolneux Grégoire, Mathoulin Simone, Fenwick Stephen, Malik Hassen, Staettner Stefan, Kissmeyer-Nielsen Peter, Mortensen Frank, Konstantidinis Ioannis, deMatteo Ronald, DeAngelica Michael, Jarnagin William,

& Fong Yuman.

PlosOne 2014

Aider la vie! INSTITUT BERGONIÉ Centre Régional de Lutte Contre le Cancer de Bordeaux et du Sud-Ouest

AARHUS UNIVERSITY

Aintree University Hospital NHS Foundation Trust

MEMORIAL SLOAN-KETTERING CANCER CENTER

- Prospective databases (RAID study)
- 288 “CARe” patients enrolled and analyzed retrospectively
- The decision to resect or to ablate was the surgeons’ privilege
- Most unresectable, borderline resectable or numerous and bilateral

Results

- 210 had synchronous CLM (73%)
- 255 bilateral (88%).
- The median number of metastases was 5 (range, 2 to 21).
- Median number of tumors resected was 2 (range, 1 to 19) and ablated 2 (range, 1 to 12).
- The median size of the largest ablated lesion per patient was 10 mm (range, 3 to 50).
- Twenty-two patients (8%) had extra-hepatic diseases.
- Median follow-up was 3.17 years (95% CI, 2.83 to 4.08)

Complications

- Mortality (3) 1%
- Beaujon series Extensive Hepatectomies: 10%
- MD Anderson: 2-stage: 2% + 6%
- Morbidity
  - 100 patients
  - 29 G1, 19 G2, 38 G3, 11 G4
  - G2+3+4 = 23.6%
  - CARe is well tolerated

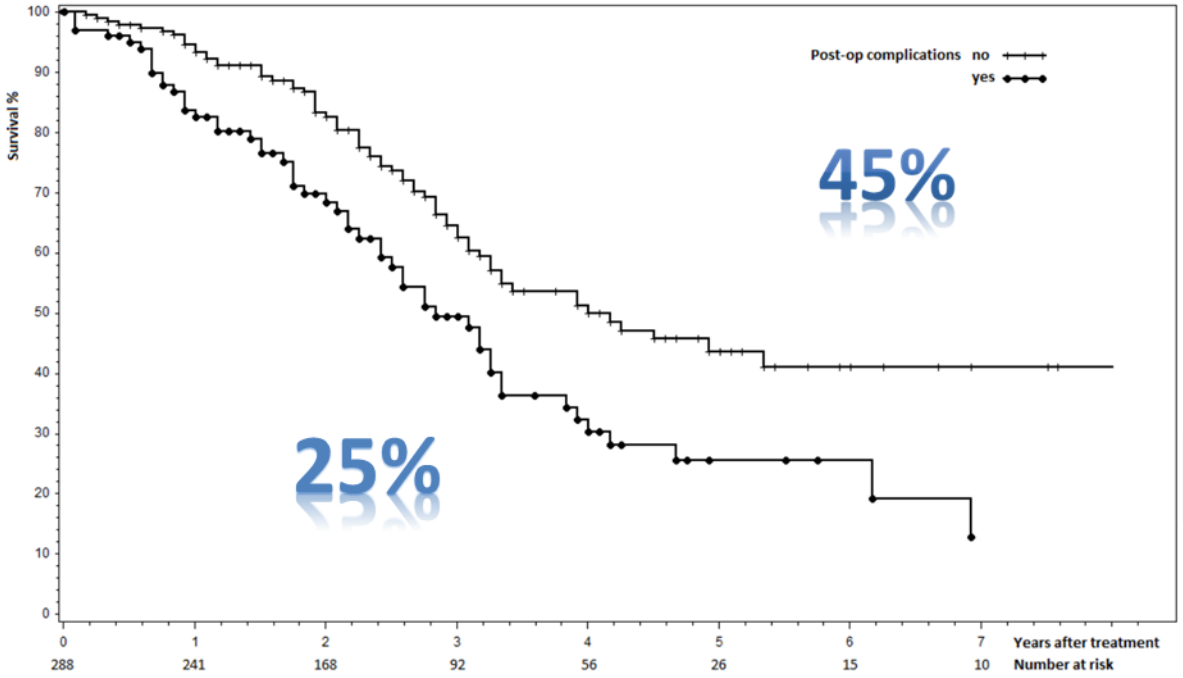
Survivals

- Median OS was 3.33y.
- 1-year LRFS rate was 90%. **No different from hepatectomy alone**
- Median PFS was 9 months .
- These results are similar to the Paul Brousse series (Adam et al 2009) with 21% Ablation and 13.5% extra-hepatic disease.

2 factors divided OS by 2

1. Extra hepatic disease: 30% 3-year OS vs 60% without

2. Post-operative complication: 5-year OS:



	Beaujon Cauchy et al 2010	MD Anderson Brouquet et al 2011	Paul Brousse Adam et al 2009	RAID study
Ablation	No	No	21%	100%
PVO	100%	70%	60%	10%
Mortality	10%	2% + 6%	0%	1%

Does CARe reduce the need for 2-stage resection?

- Cost-Effectiveness of Simultaneous Resection and RFA Versus 2-stage . Hepatectomy for Bilobar Colorectal Liver Metastases (Abbott et al 2013)
- Cost-effectiveness analysis revealed that resection/RFA cost $37,120 for 46.2-month survival, while planned 2-stage resection cost $62,198 for 35.9-month survival.

Time for surgical de-escalation?

- For healthy parenchyma: clearly **YES**
- For CLM: clearly **NO**. The therapeutic escalation must go on, both medically (new conversion regimen, intra-arterial route, etc.)and surgically
- After AR, NAR and 2 stage resection,

CARe is the rest of the story, the new standard of ….care for advanced CLM!

Last contributions

- MD Anderson
  - Mise et al: Ann Surg 2016
- Memorial
  - Kingham et al JAMCollSurg 2015

For what patient benefit?

- *overall survival?*
  - Solitary CRLM: 5-year OS is 65%
  - Bilateral CRLM: between 40 to 51%
  - Bilateral CRLM + 8% Extra Live mets: 37% (Evrard)
  - Bilateral CRLM + 13% Extra Liver mets: 33%(Adam)
- 40 months OS in the chemo group of the CLOCC trial! And no difference with the surgical group
- There is a threshold for surgical forcefulness

For what patient benefit?

- PFS ?
  - Of course, compared with a chemo arm
  - PFS is quite low as CRLM is a recurent disease
  - 13 to 19% PFS at 3 years: 8 or 9 patients will recur!
- Is it Quality of Life?
  - Yes in the ARF2003 study but low compliance to fulfill the questionnaire
  - QoL is correlated to PFS!
  - By increasing PFS, surgery could increase QoL!

For what patient benefit?

- Is it to go to a chronic illness?
  - Initial debulking surgery
  - Several lines of chemo
  - Than non invasive local treatments (RF, stereotaxy, HIFU etc.)

Take home message

- Management of CRLM (especially for advanced stages) is complex
- We absolutely need a multidisciplinary approach
- For that, a common knowledge basis is mandatory between biologists, oncologists and surgeons.