UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE
Département de chirurgie

Hôpitaux Universitaires Genève

Nodule du foie découvert lors d'investigations de rectorragies

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Journée médecin généraliste 2023

Message clé

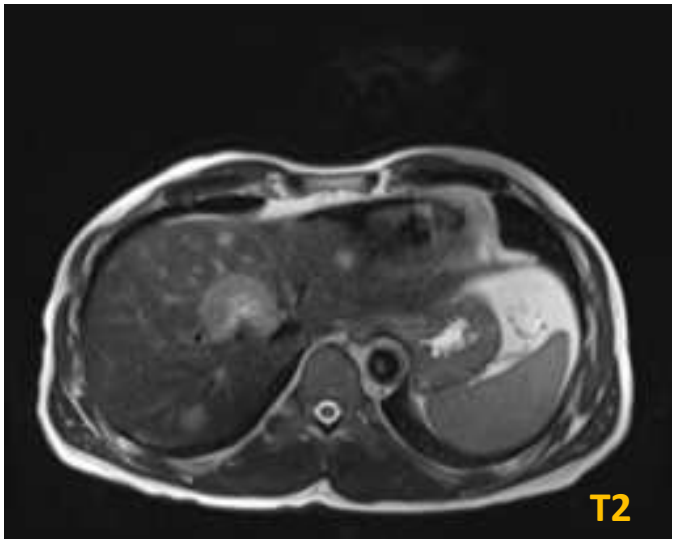
- Pas si loin le temps où le CCR ne faisait qu'une seule entité.

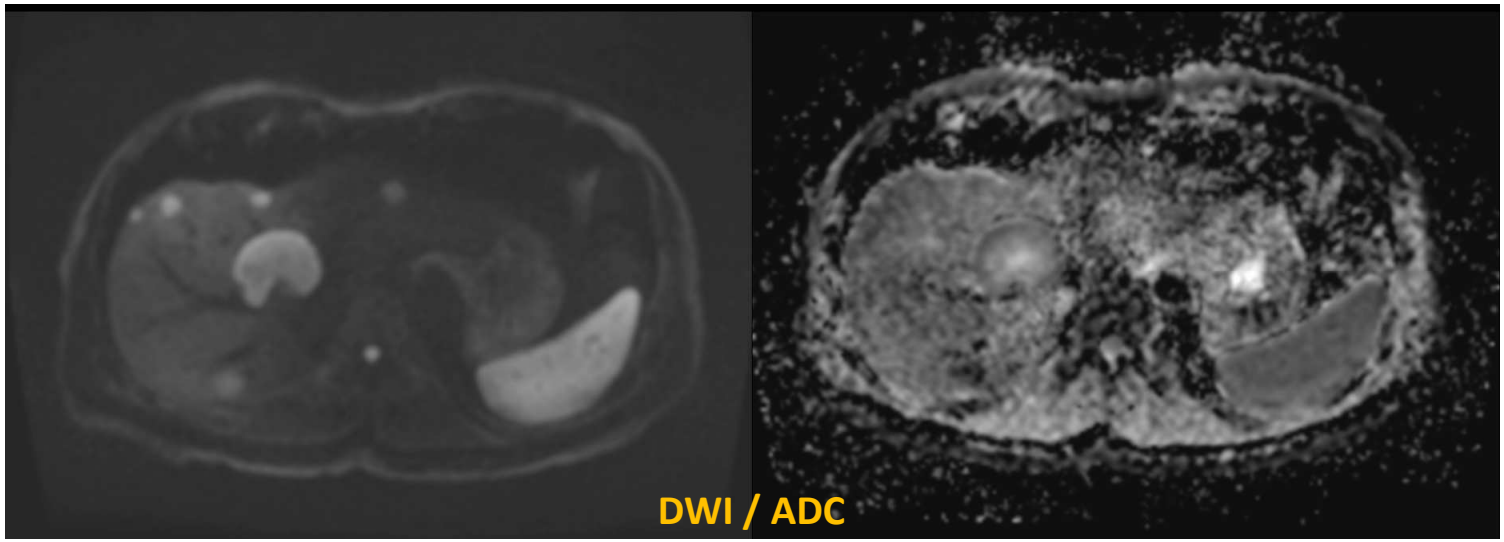
Aujourd'hui,

- Une meilleure compréhension de la biologie tumorale permet de définir des sous-types de CCR ayant une valeur pronostique et prédictive d'efficacité thérapeutique.
- Les progrès thérapeutiques et l'affinement diagnostique rendent le choix thérapeutique beaucoup plus ciblé (oncologie de précision) avec en corollaire une nette amélioration de la survie des patients.
- Même avec un stade métastatique, une approche curative peut être proposée et se base sur une approche multidisciplinaire.

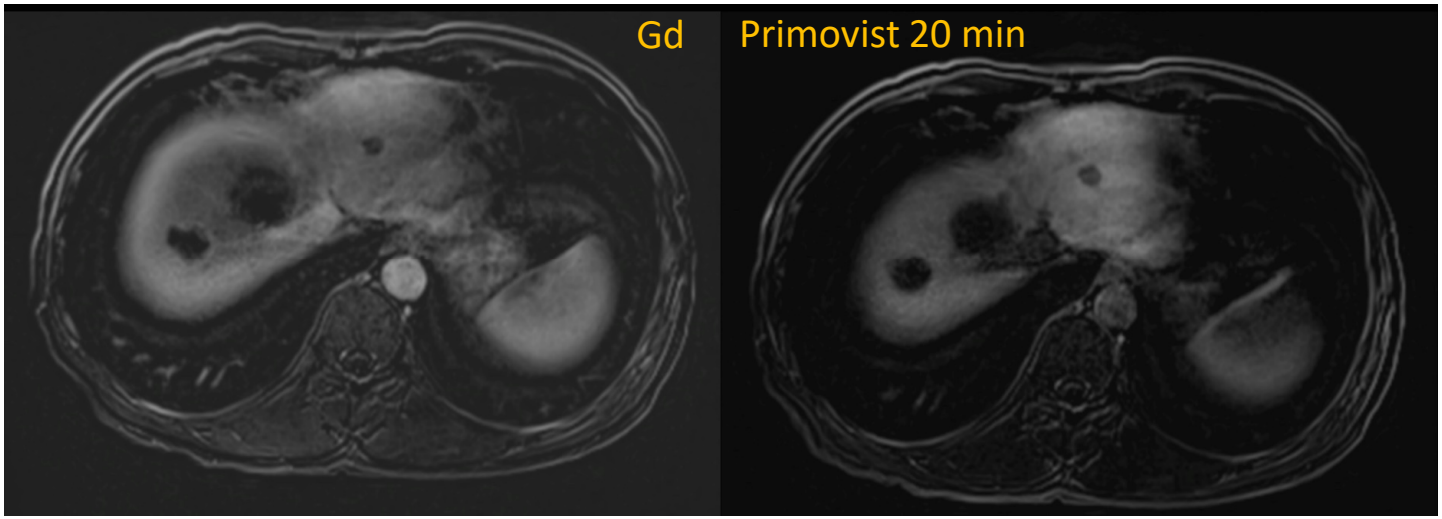
Histoire du patient

- Homme, 55 ans
- Aucun antécédent
- Coloscopie pour hématochézie
  - Adénocarcinome de la charnière recto-sigmoidienne (17-20 cm de la marge anale)
- Bilan d'extension
  - CEA: 102 µg/l
  - CT thoraco-abdominal: multiples lésions hépatiques d'allure secondaire

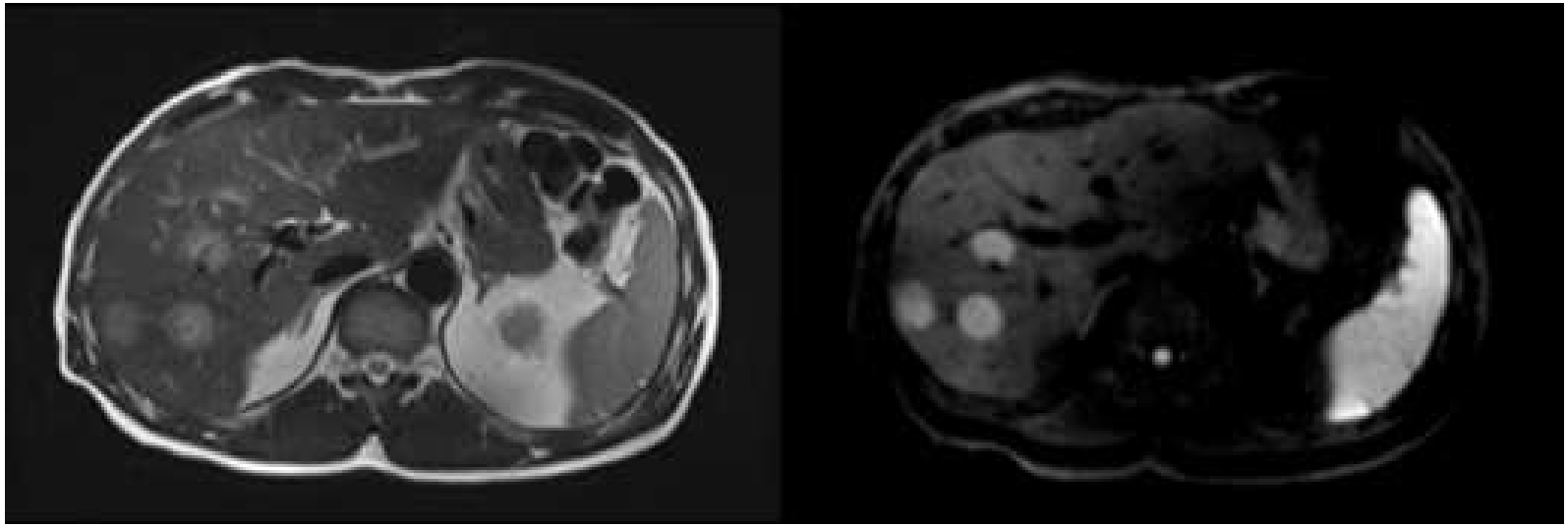


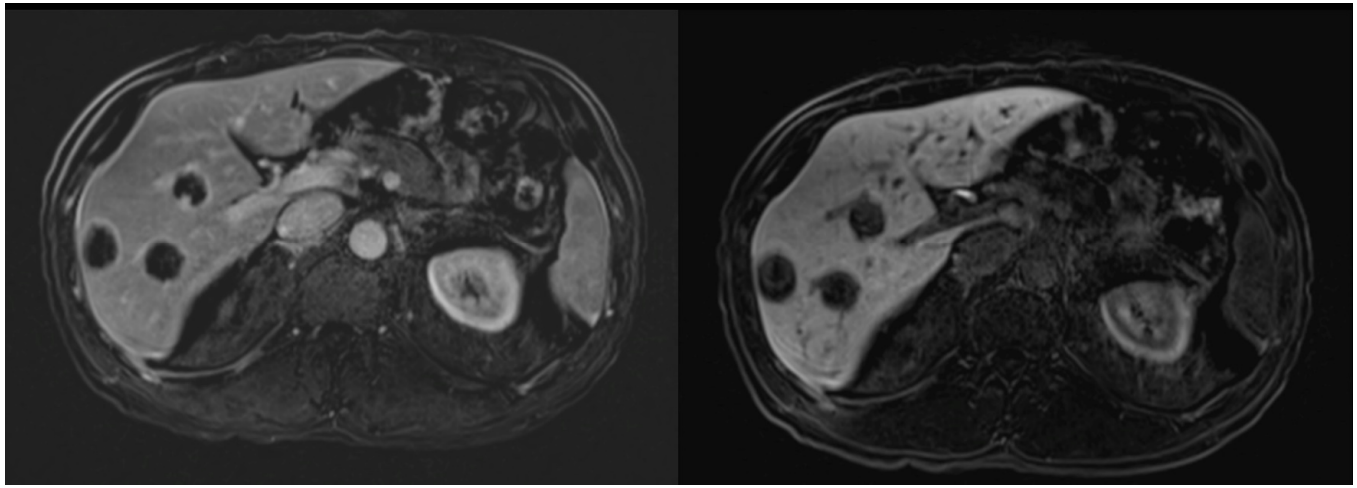


14 lésions hépatiques touchant tous les segments hépatiques → 4 lésions dans le foie gauche (segments II, III et IV)



- Hypersignal T2, restriction de la diffusion
- Rehaussement périphérique
- Absence de captation du primovist à 20 min (absence d'hépatocytes fonctionnels)



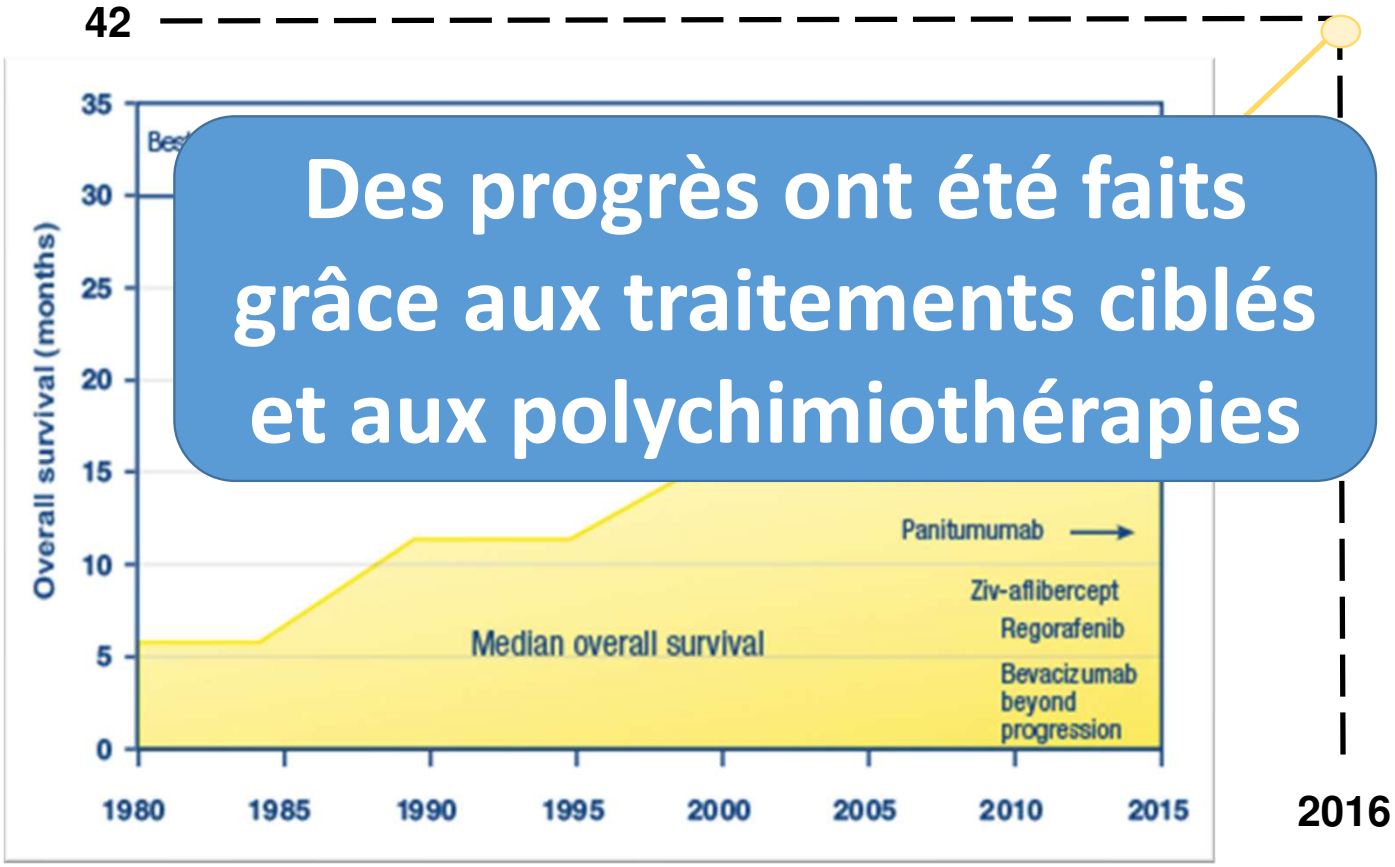


→ Anomalies évocatrices de multiples lésions secondaires hépatiques

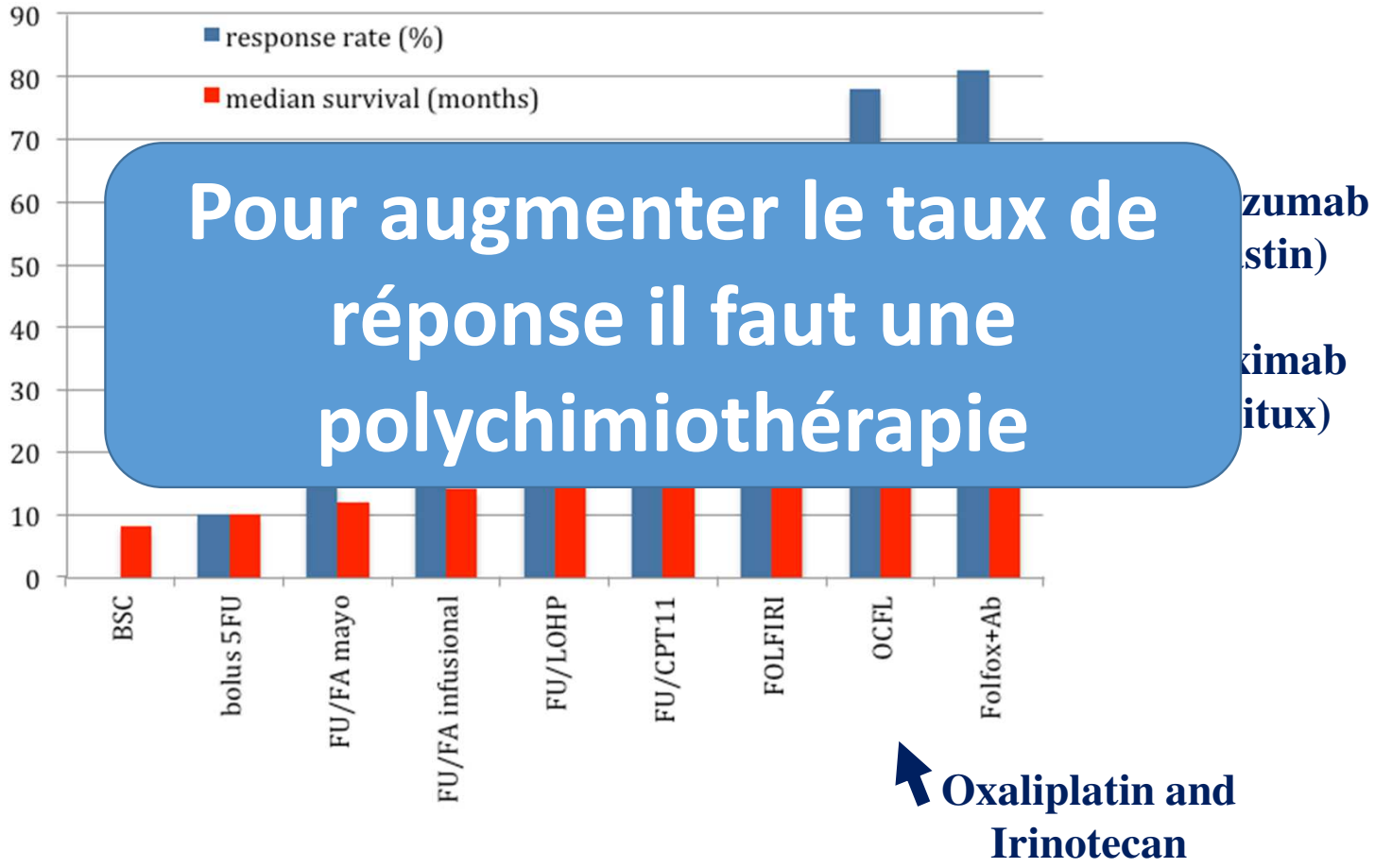
Que faut-il faire en premier?

- Chirurgie du foie +/- thermoablations percutanées hépatiques
- Chirurgie colique
- Traitement endovasculaire hépatique
- Chimiothérapie
- Traitement palliatif

La chimiothérapie seule ?

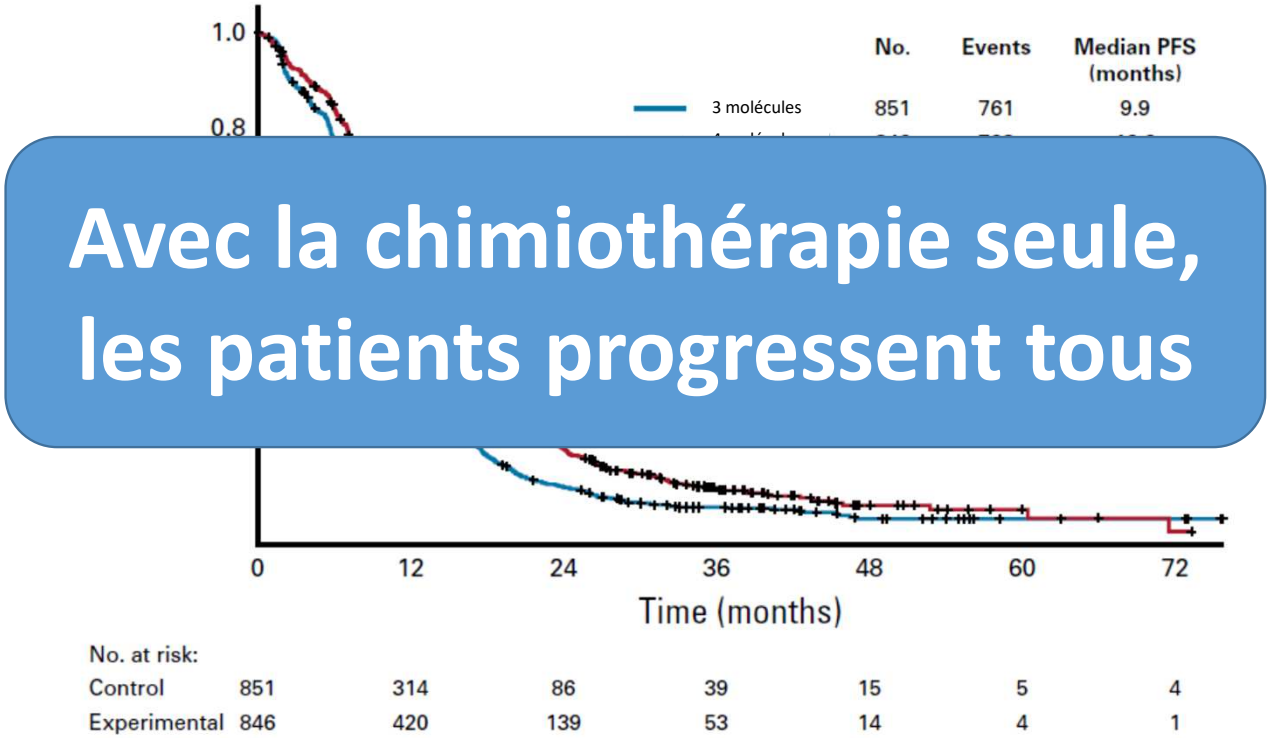


La chimiothérapie seule ?



La chimiothérapie seule ?

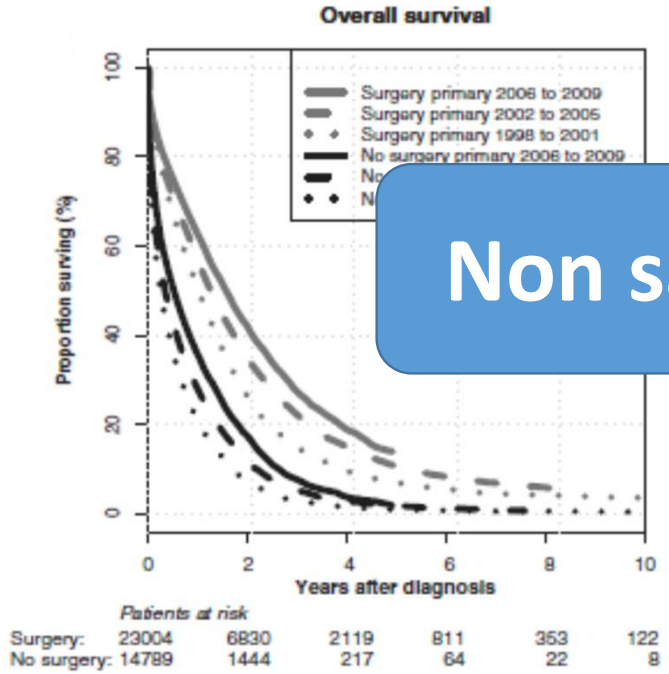
Récidive



Avec la chimiothérapie seule, les patients progressent tous

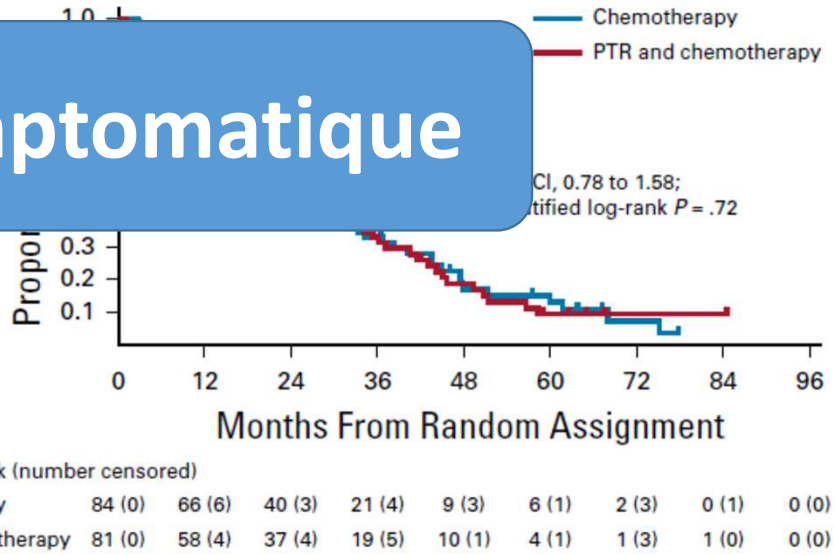
Cremolini *et al*, JCO, 2020

La chirurgie du primaire ?



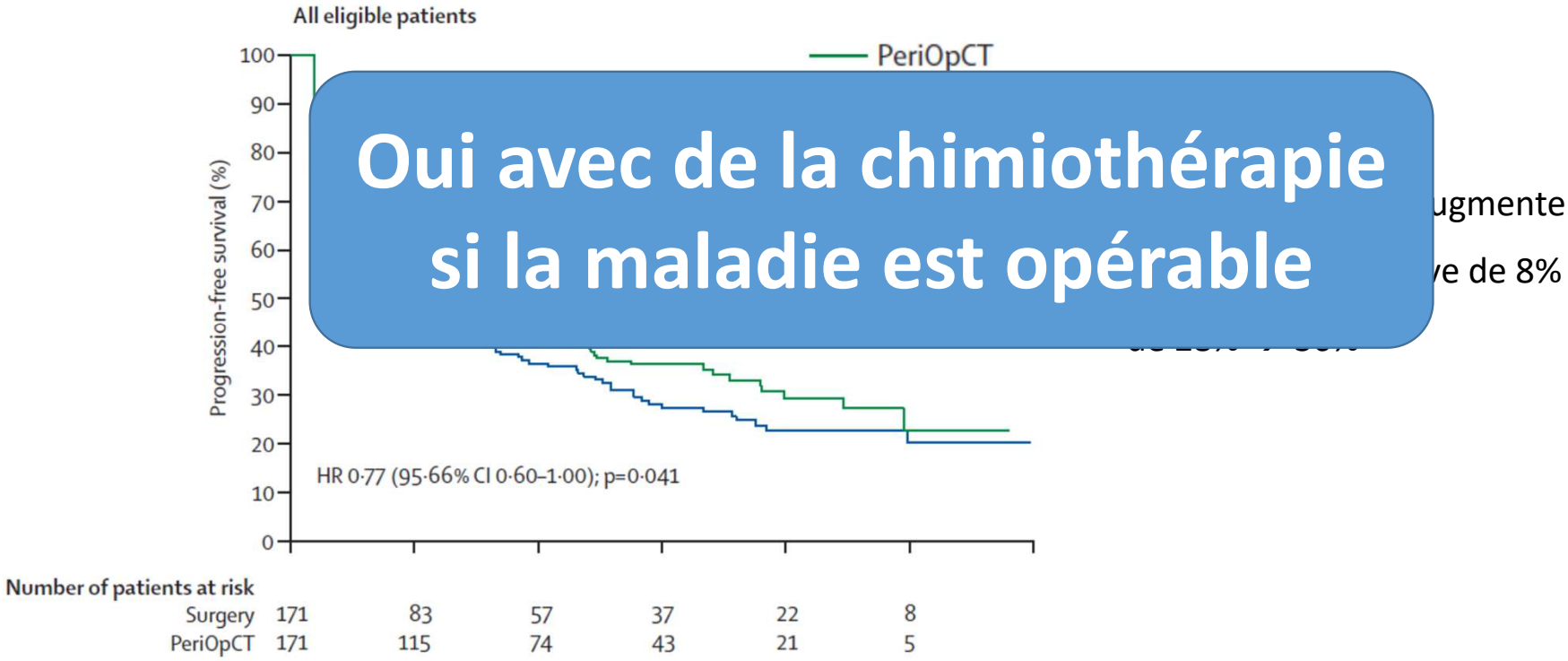
Tarantino *et al*, Ann Surg, 2015

Non sauf si symptomatique



Kanemitsu *et al*, JCO, 2021

La chirurgie du foie seule?



Oui avec de la chimiothérapie si la maladie est opérable

ugmente

ve de 8%

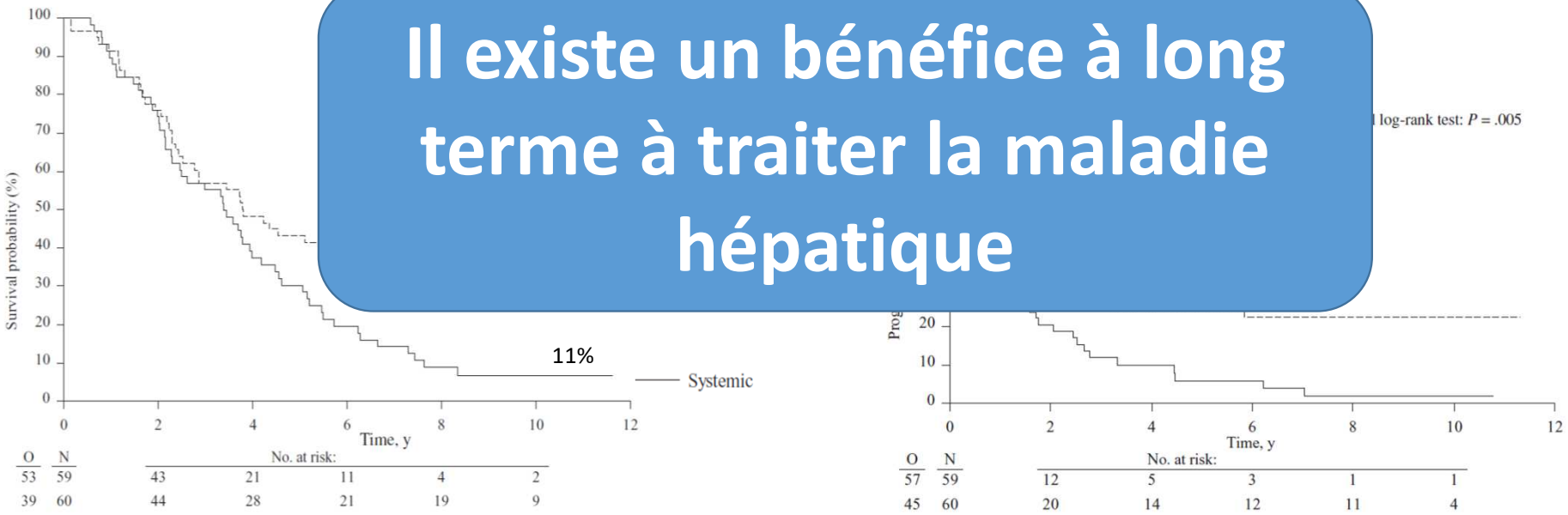
Nordlinger *et al*, Lancet, 2008

Traitements locaux + Chimiothérapie

Survie globale

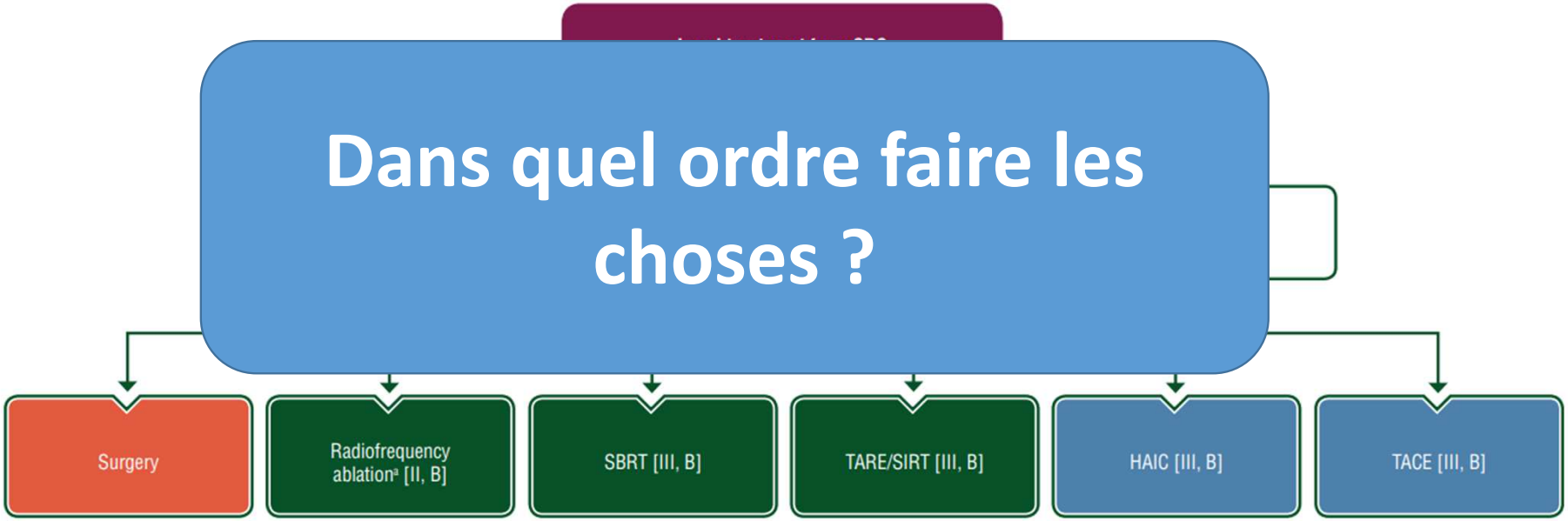
Récidive

Il existe un bénéfice à long terme à traiter la maladie hépatique



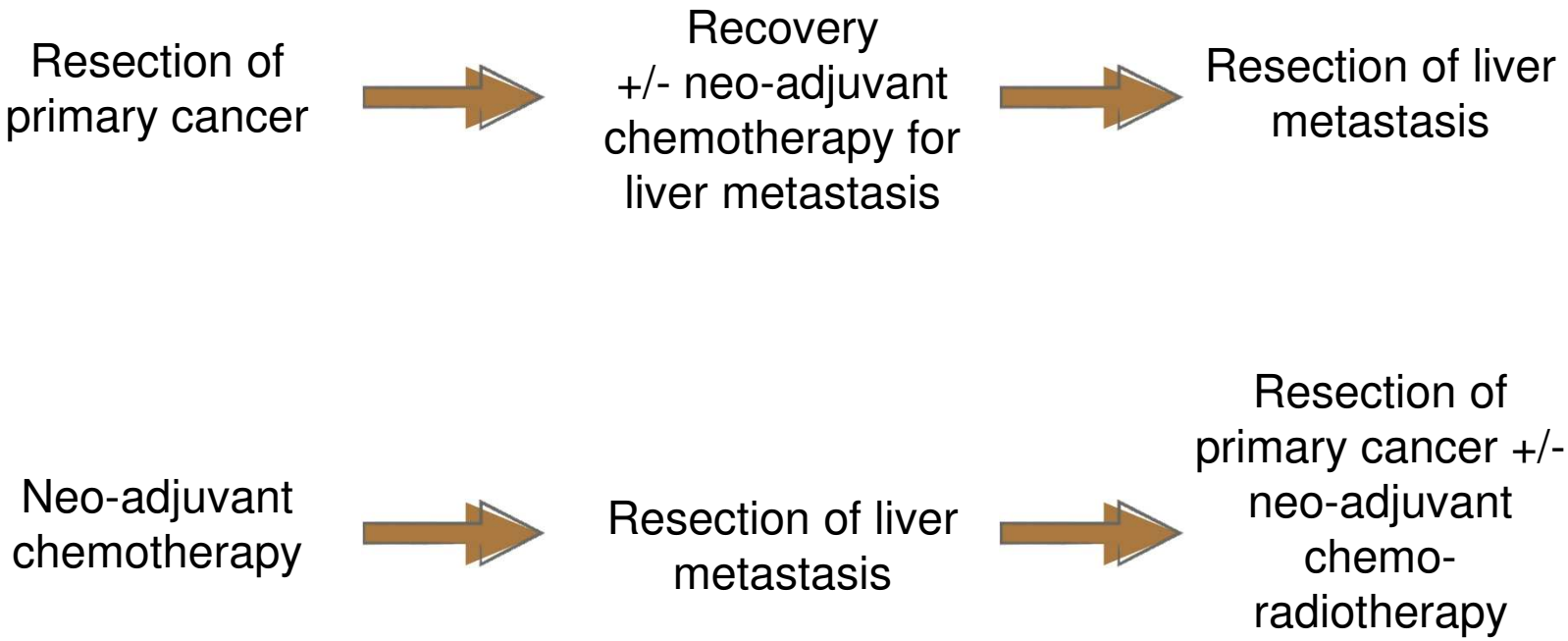
Ruers *et al*, JNCI, 2017

Traitements locaux



Cervantes *et al*, Annal of Oncol, 2023

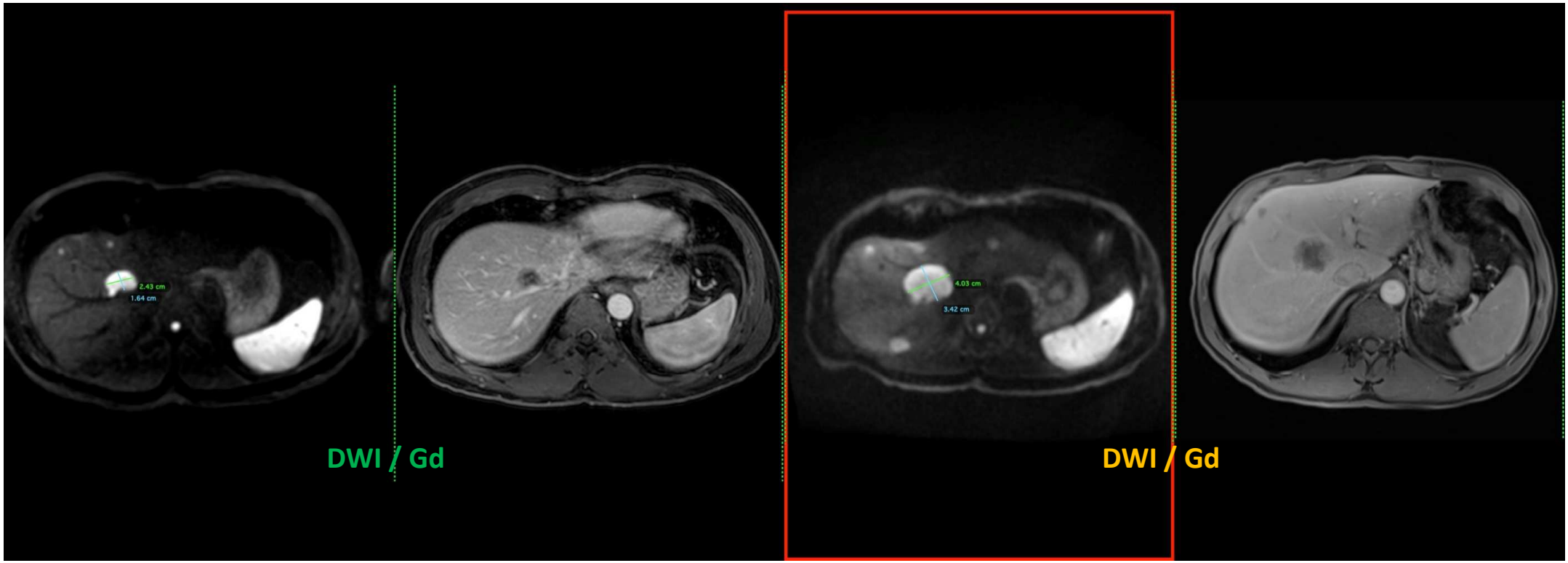
Synchronous liver metastasis



Histoire du patient

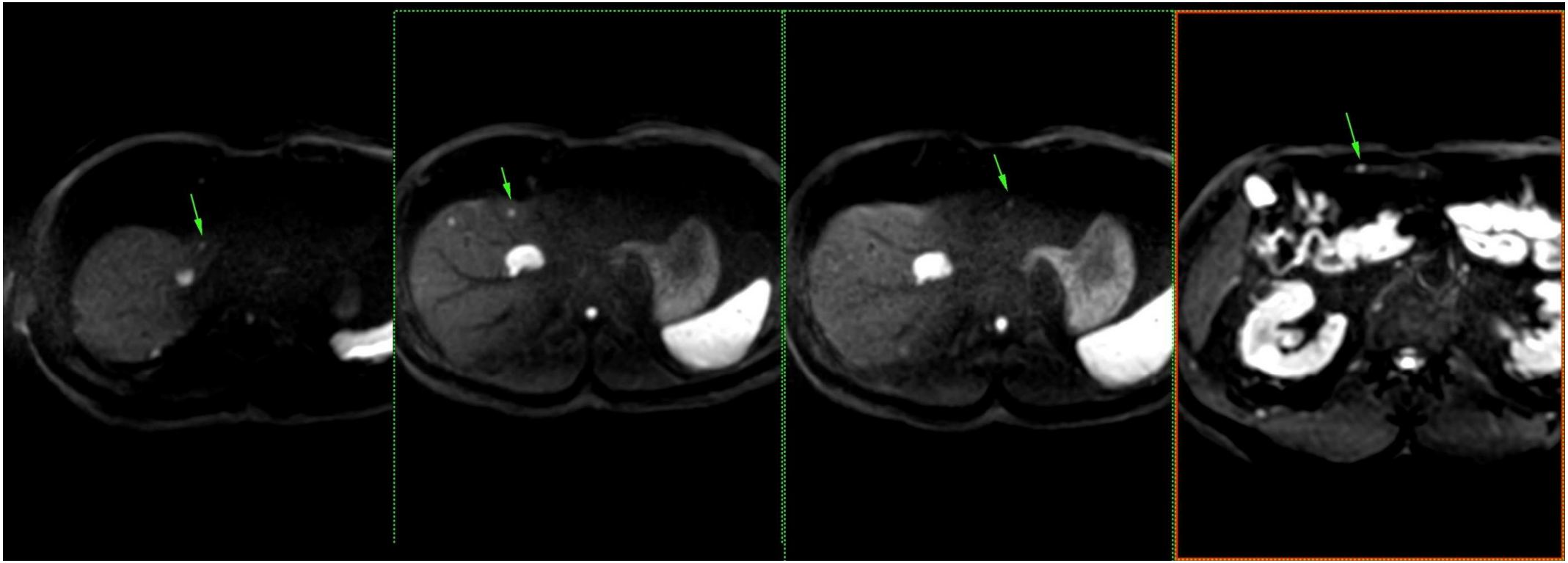
- Chimiothérapie par Folfiri-Vectibix pendant 2 mois
- Bonne réponse biologique et radiologique
- CEA: 12 µg/l

Contrôle à 3 mois post chimiothérapie



Diminution en taille de toutes les lésions hépatiques de + de 30% de diamètre : réponse partielle selon RECIST 1.1

Contrôle à 3 mois post chimiothérapie



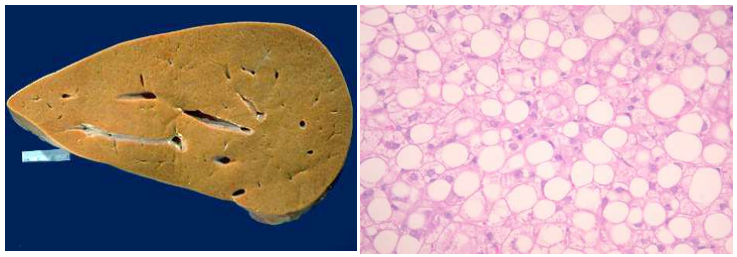
Persistance de 4 lésions millimétriques du foie gauche
→ Une du segment IV a
→ Deux du segment II
→ Une du segment III

Comment gérer la chirurgie du foie en présence de multiples métastases?

- Chirurgie en deux temps avec embolisation portale préalable
- ALPPS (Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy)
- Radioembolisation lobaire (=SIRT)
- Transplantation

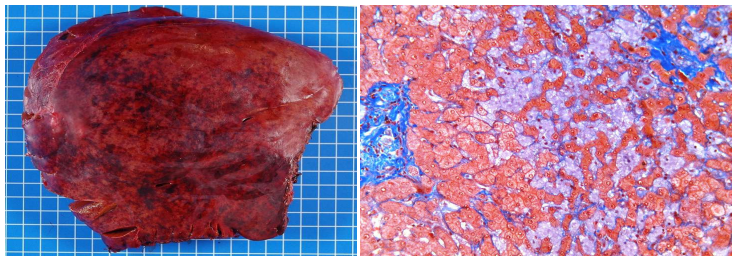
Chemotherapy associated liver injuries (CALI)

CASS: Chemotherapy associated simple steatosis



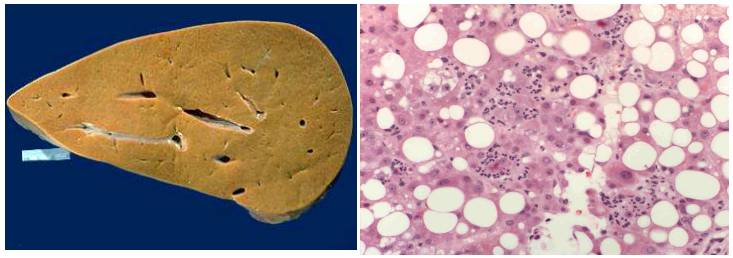
- Lipids accumulation without inflammation
- Related to 5-FU and Leucovorin

Sinusoidal obstruction syndrome (SOS), NRH: Chemotherapy associated sinusoidal lesions



- Rupture of sinusoidal wall integrity
- Related to oxaliplatin

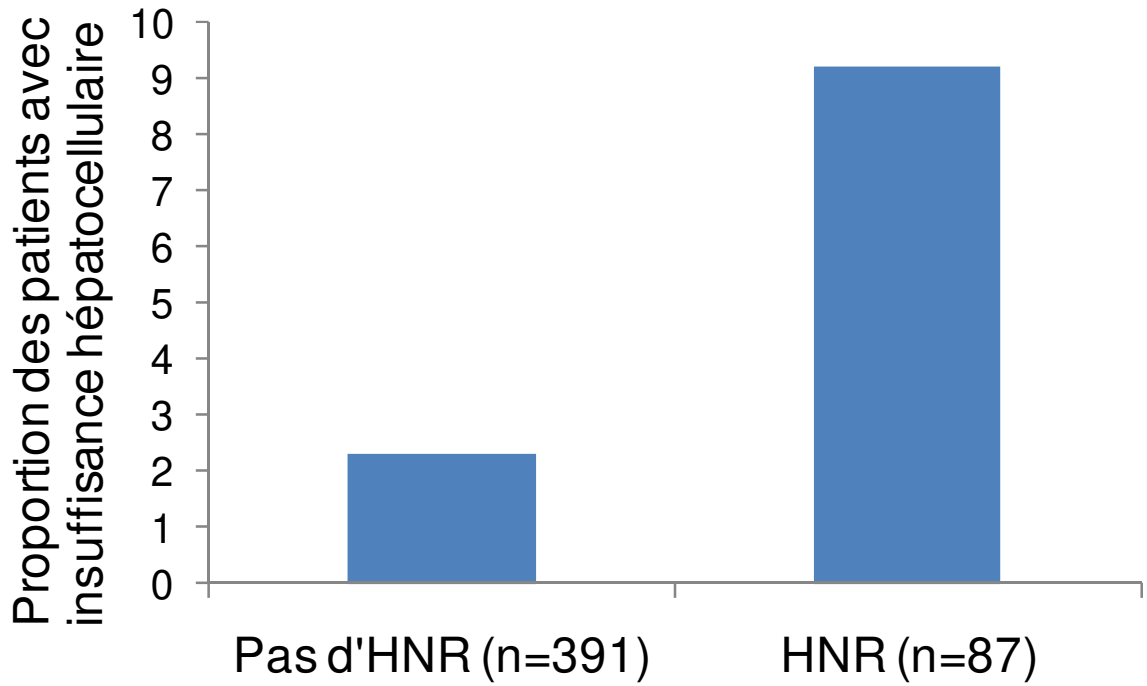
CA$H: Chemotherapy associated steatohepatitis



- Lipids accumulation, ballooning and inflammation
- Related to irinotecan

Rubbia-Brandt L et al, Ann Oncol 2004
Rubbia-Brandt L, Clinical liver dis 2010
Mentha G, Sem Liver Dis 2013
Zorzi et al. BJS 2006

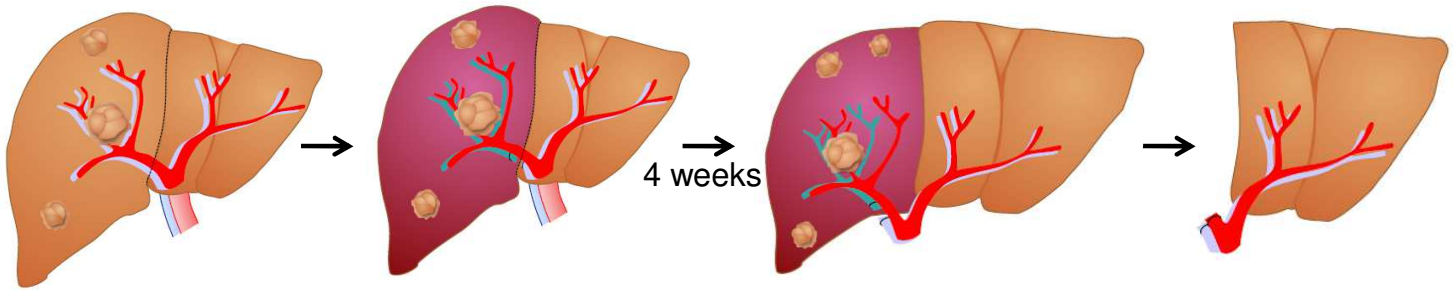
Chemotherapy-induced liver injury:



*defined as bili >50mg/dl and/or Quick <50% on Day 5

Rubbia-Brandt L et al. Histopathology 2010
Vigano L et al, Ann Surg Oncol 2015

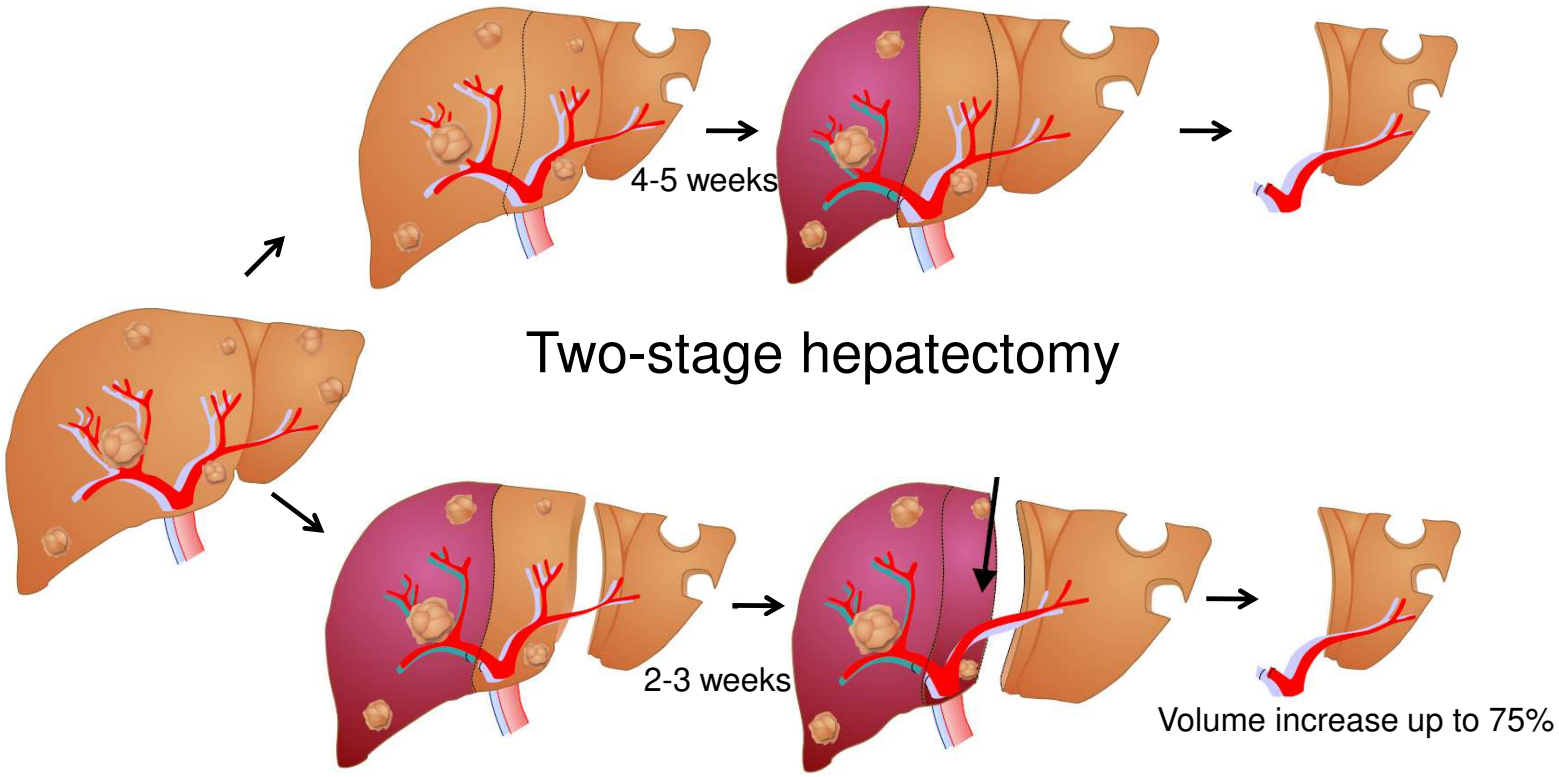
Surgical strategy: portal vein embolisation



Embolisation

Volume increase
of 8-34%

Surgical strategy: portal vein embolisation



ALPPS: Associating Liver Partition and Portal vein ligation for Staged hepatectomy

Histoire du patient

- Embolisation portale droite

- Hépatectomie droite par laparotomie
- Hépatectomies atypiques dans les segments III (1 métastase) et II (2 métastases)
- Ablation radiologique d'une métastase du segment IV

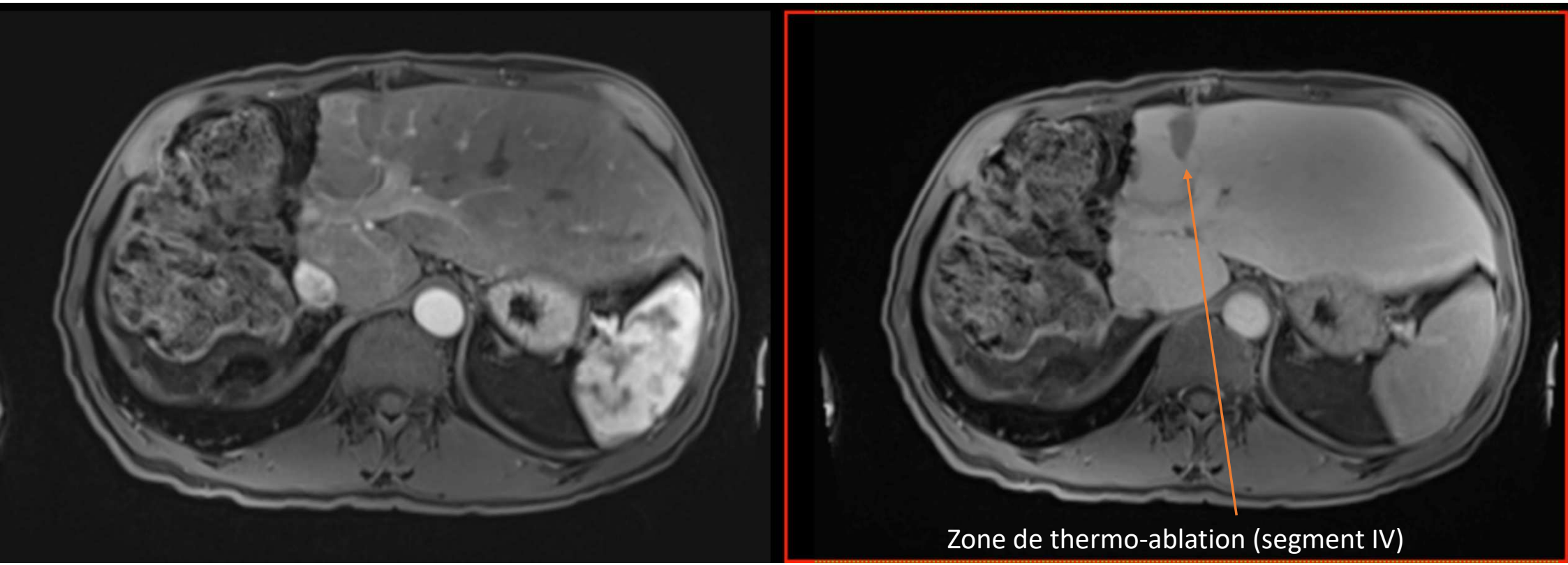
Embolisation portale droite

Pré- traitement

Post-traitement

- Intervention sous AG
- Ponction trans-hépatique sous guidage US de la veine porte
- Occlusion de la circulation veineuse portale du foie droit par un agent liquide d'embolisation
- Hospitalisation de 48h au décours
- Risques: hémorragiques, infectieux, douleurs
- Objectif : hypertrophie controlatérale -> évaluation à 4 semaines par CT ou IRM

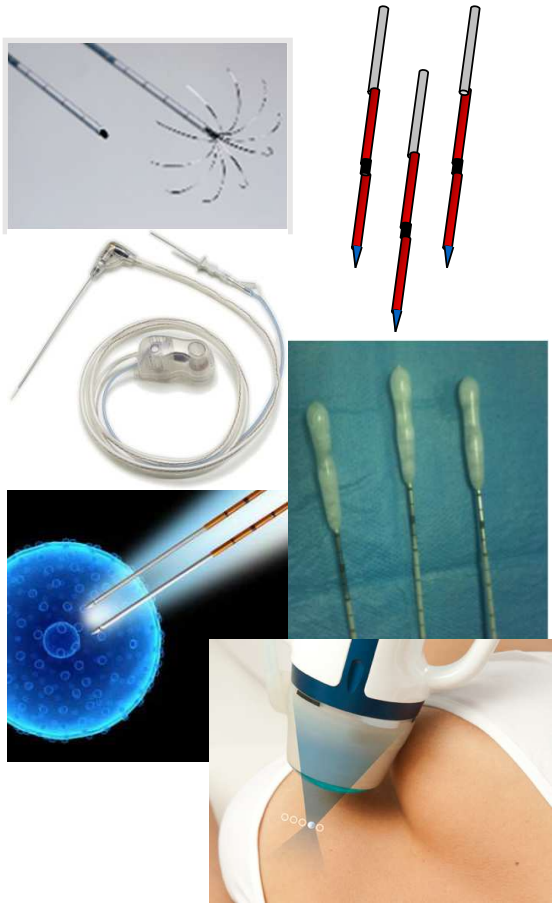
IRM hépatique de suivi post thérapeutique à 6 mois

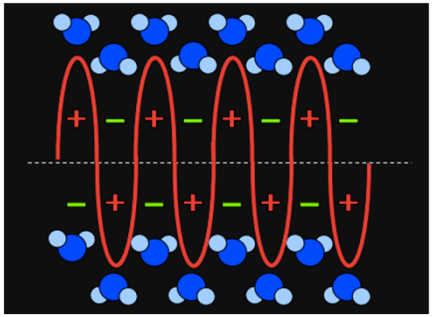


Plage avasculaire à contours géométrique du segement IV
Absence de prise de contraste nodulaire
Marges satisfaisantes entre 5 et 10mm
Imagerie en faveur d'une ablation complète

Techniques d’ablations percutanées

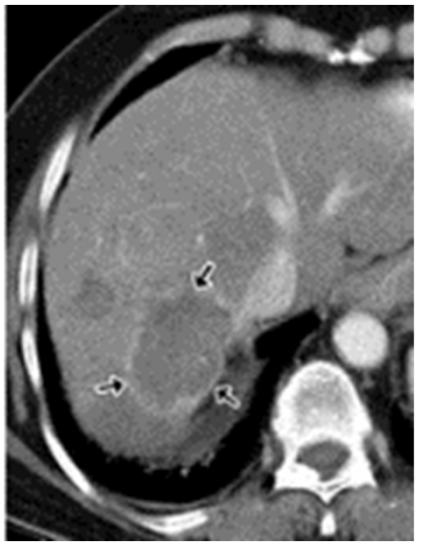
- Radiofréquence Mono / Multipolaire
- Micro-ondes
- Cryoablation
- Electroporation Irreversible
- HIFU (High Intensy Focused Ultrasound)
- Traitements combinés





Micro-ondes

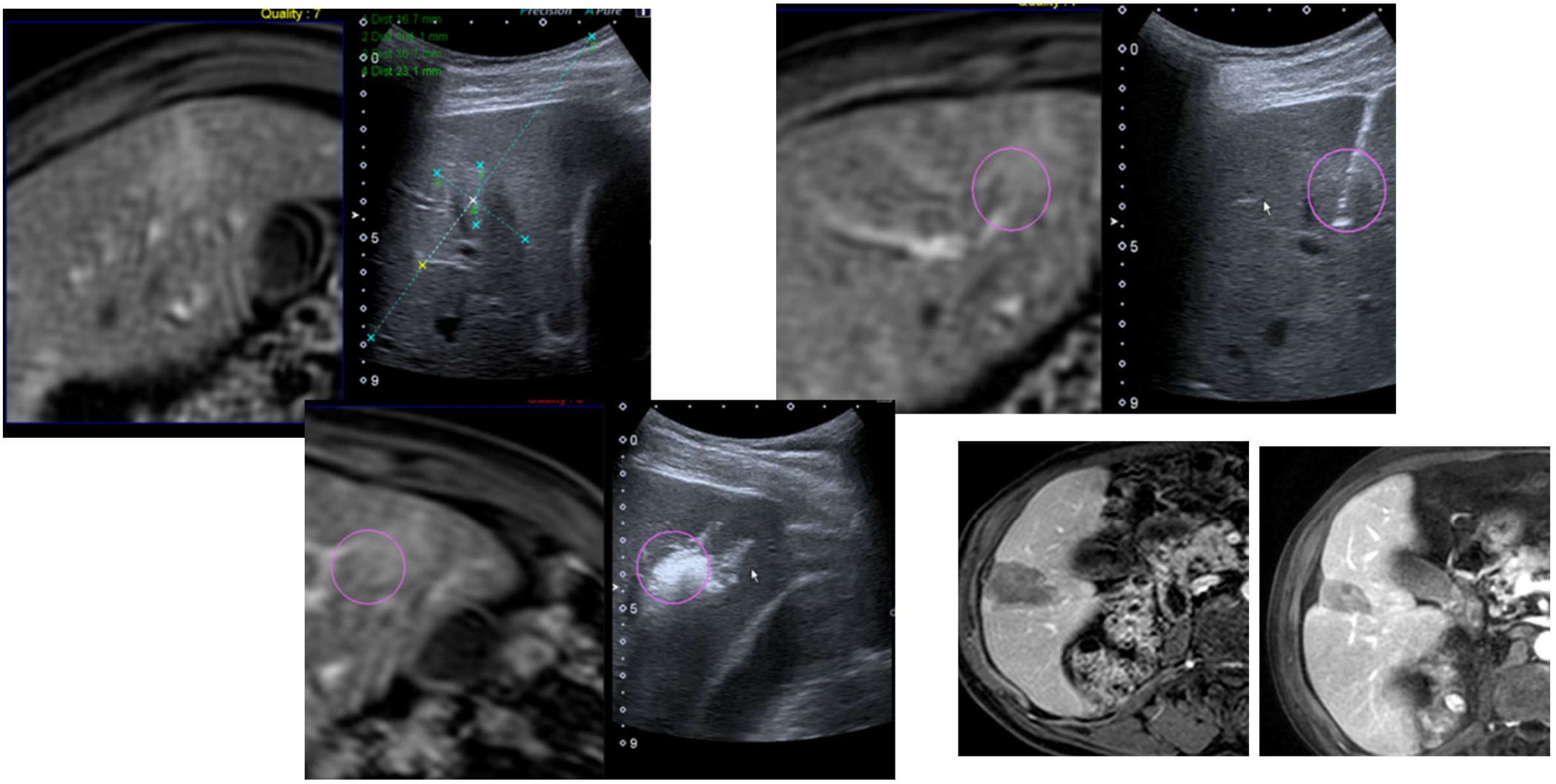
- Décrit en 1986 par Tabuse (Japon) , applications au foie en 1990
- **900Mhz à 2450 Mhz**
- Energie cinétique H2O → Energie thermique



Plusieurs avantages théoriques sur la RF :

- Zone ablation plus importante
- Plus chaud **160 à 180° C**
- Plus vite : environ 5 à 10 min d'abaltion
- Moins sensible au « heat sink effect »

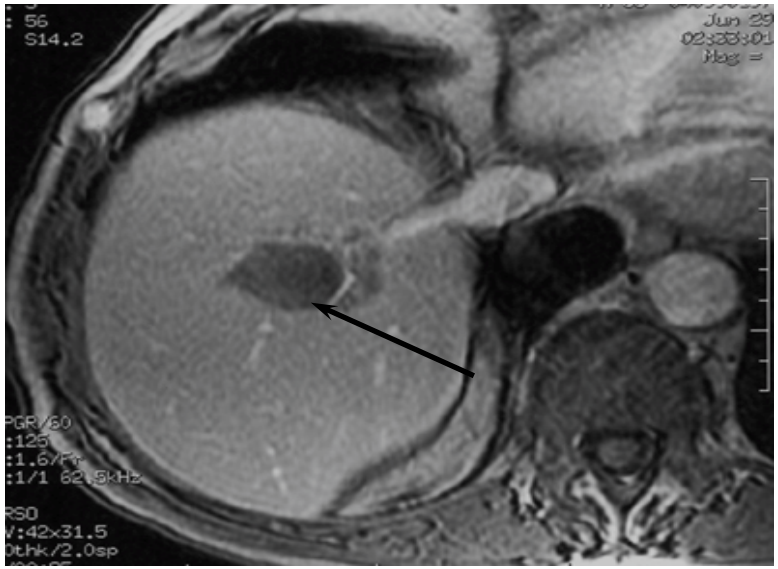
Thermo-ablations percutanées : mode de guidage



Limitation technique: micro-ondes

Proximité de vaisseaux

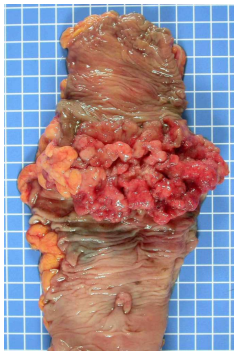
Risque de ne pas détruire des cellules tumorales
au contact des vaisseaux de diamètre > 4mm
« heat sink effect »



Quelles solutions:

- Occlusion temporaire du vaisseau cible
- Embolisation tumorale préalable
- Si impossible, autres techniques interventionnelles :
  - Radioembolisation (SIRT)
  - Chimiothérapie intra artérielle hépatique (lésions diffuses)
  - Electroporation irréversible
- Alternatives thérapeutiques : SBRT, traitement systémique

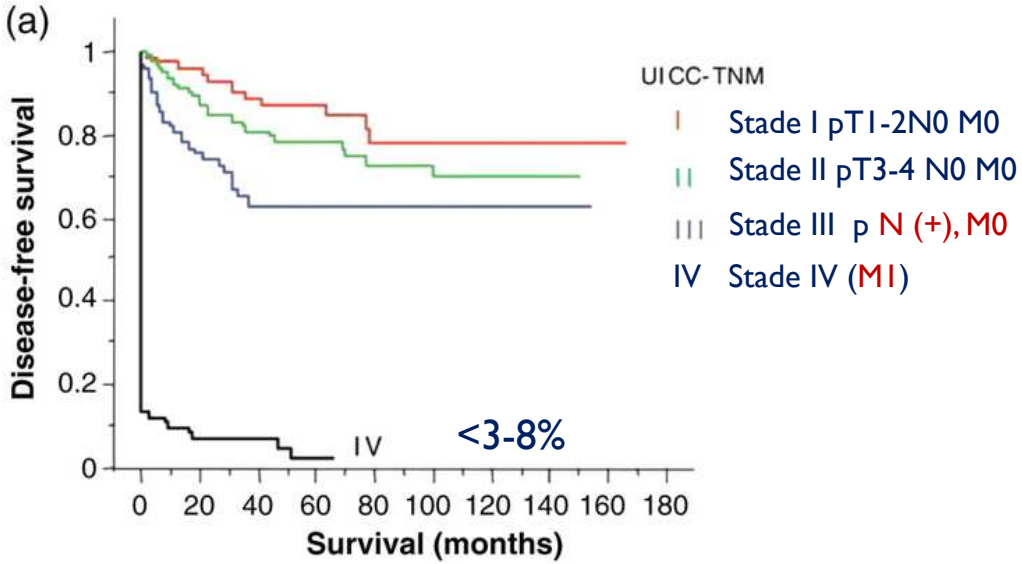
Pathology



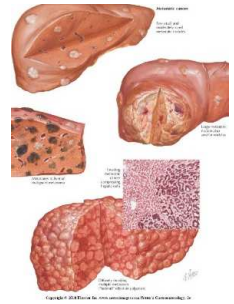
Metastases: highly contribute to mortality of CRC

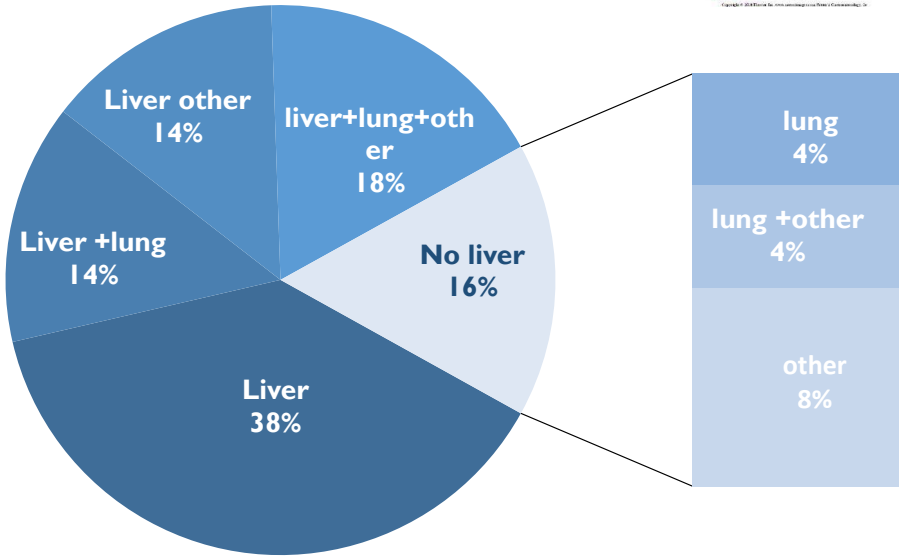
20% patients : synchronous
40% patients : metachronous

Pathologic stage and 5-y survival

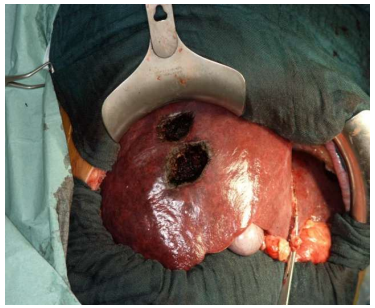


Major site : Liver





Weiss et al J Pathos 1986
N=801 autopsies

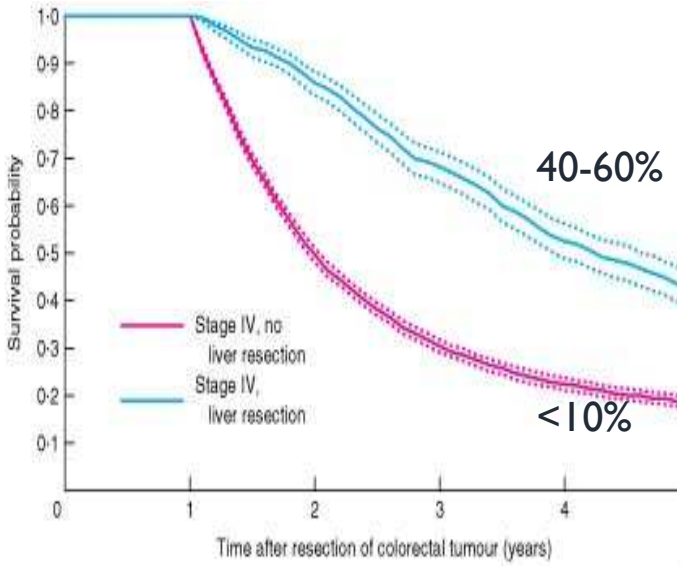


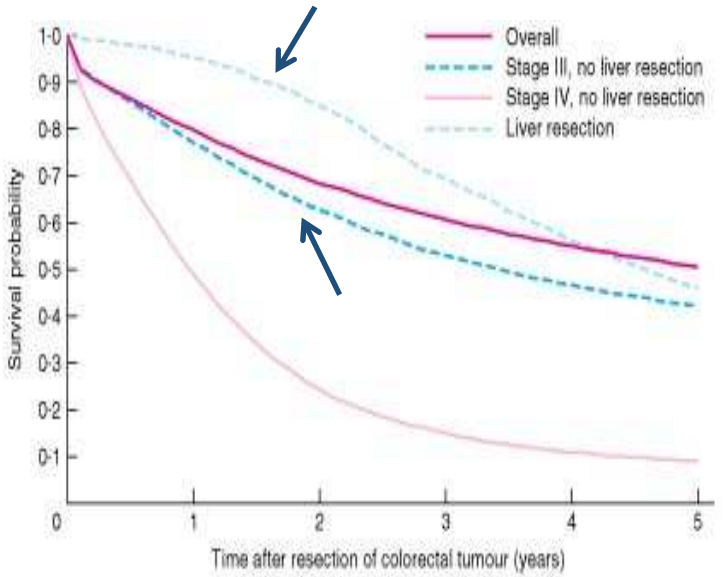
Surgical management and outcomes of colorectal cancer liver metastases

E. J. A. Morris[1], D. Forman[1,2], J. D. Thomas[1], P. Quirke[3], E. F. Taylor[1], L. Fairley[2], the late B. Cottier[4] and G. Poston[5]

British Journal of Surgery 2010; 97: 1110–1118

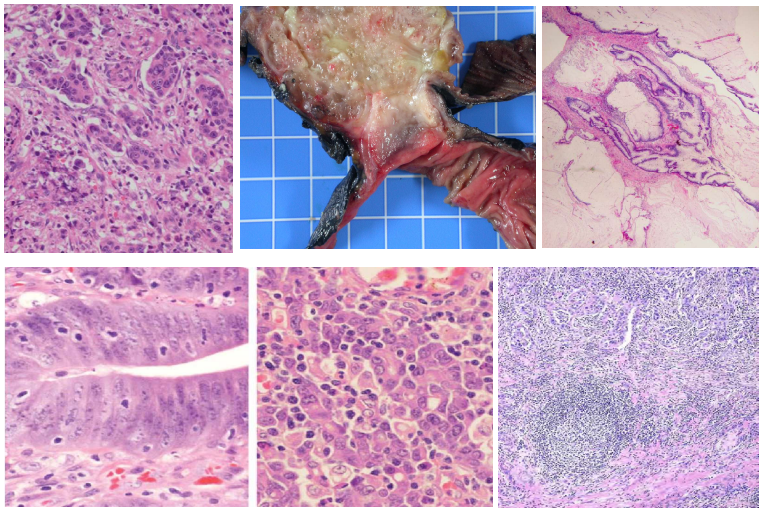
Surgical resection of HCRM (stage IV): only ttt associated with long-term survival (comparable to stage III)

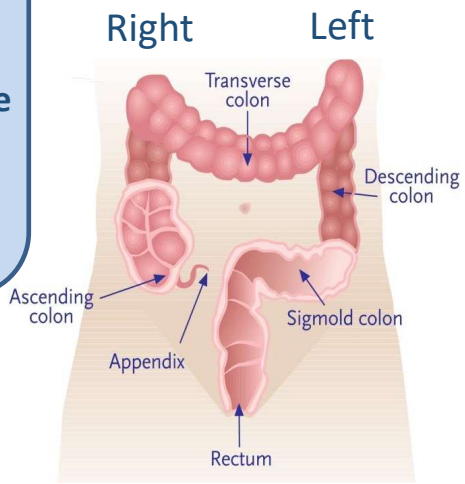




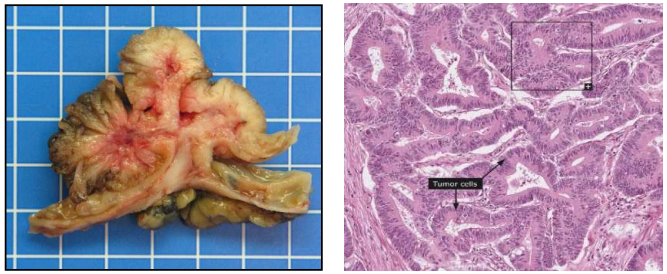
Tumors in proximal colon (right side) and distal colon (left side) exhibit different characteristics

Woman,
Large (pT3) N0 M0
Poorly differentiated, medullary or mucinous AK
Crohn's- tumor or high tumor infiltrating lymphocyte
Peritoneal carcinomatosis
Better overall survival in stage I and II
Worse overall survival stage III and IV





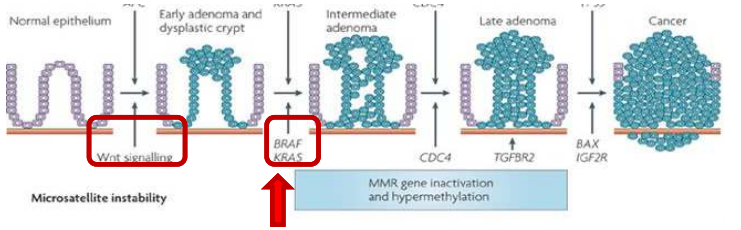
Men,
N+M+
Well differentiated tubulo-villous or classic AK
Little lymphocytic infiltration
Rarely mucinous
Liver and lung metastasis
Worse overall survival in stage I and II
Better overall survival stage III and IV



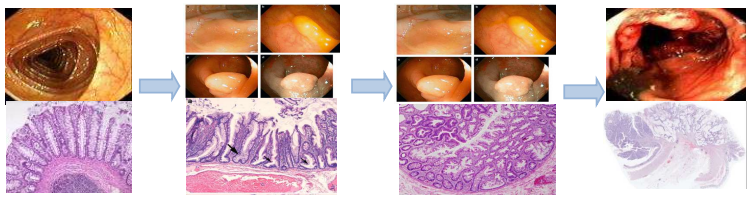
Tumors in proximal colon (right side) and distal colon (left side) exhibit different molecular pathways

MSI morphology

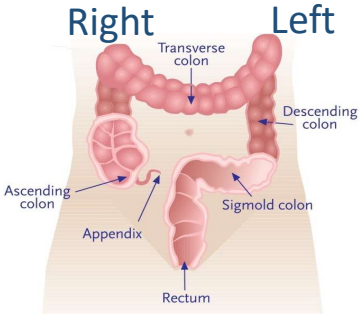
MSI pathway 16%



Serrated polyp d to carcinoma

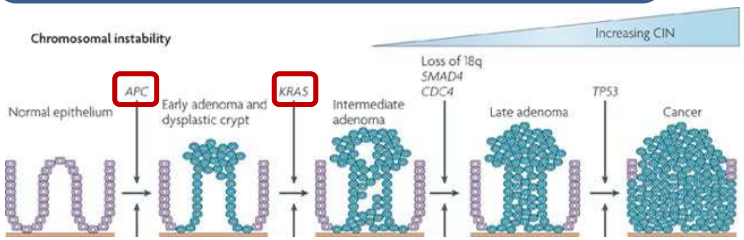


Normal mucosae | Sessile serrated Polyp | Sessile serrated polyp with dysplasia | Colorectal cancer

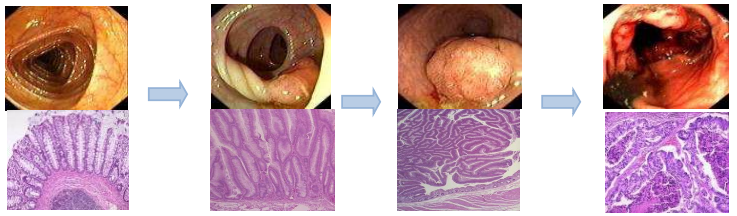


MSS morphology

CIN pathway 84%



Conventional adenoma to carcinoma



Normal mucosae | Low grade dysplastic adenoma | High grade dysplastic adenoma | Colorectal cancer

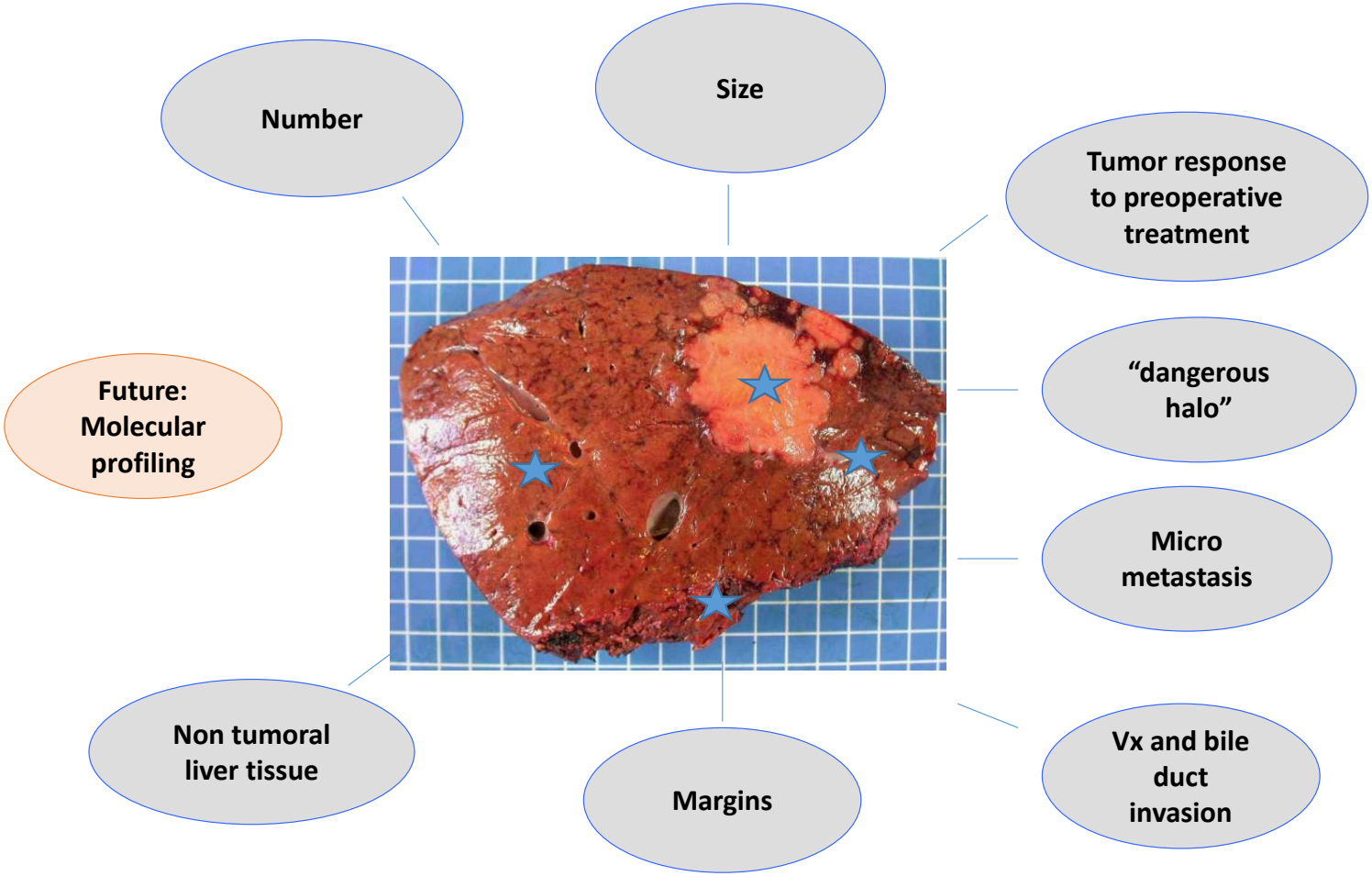
Do not respond well to conventional chemotherapies, but demonstrate results with immunotherapies because these tumors have high antigenic load.

Benefit more from adjuvant chemotherapies such as 5-fluorouracil (5-fu)-based regimes, and targeted therapies such as anti- epidermal growth factor receptor (EGFR) therapy

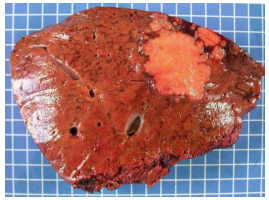
MSI, BRAF and RAS molecular status in CRC

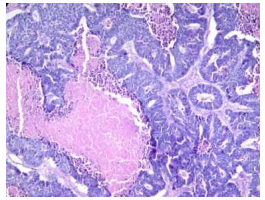
- Provide valuable prognostic and predictive information
- Increasingly used in clinical decision-making
- Pathologists can easily recognize these tumor types.

Pathology examination of CRLM: potentially important prognostic factors



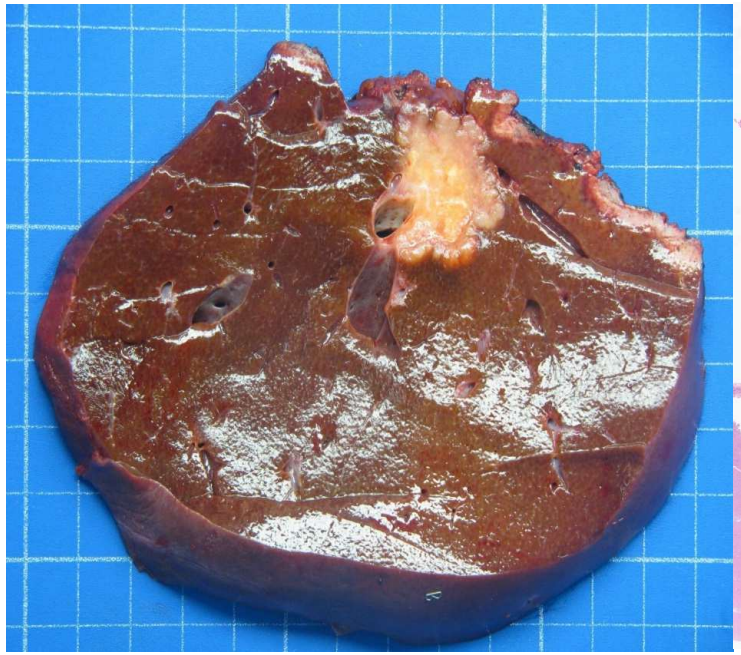
Today…

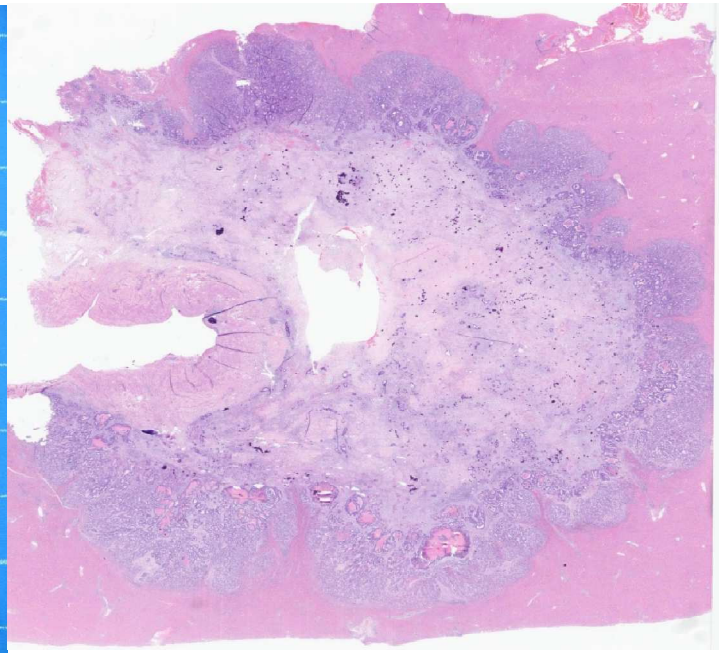


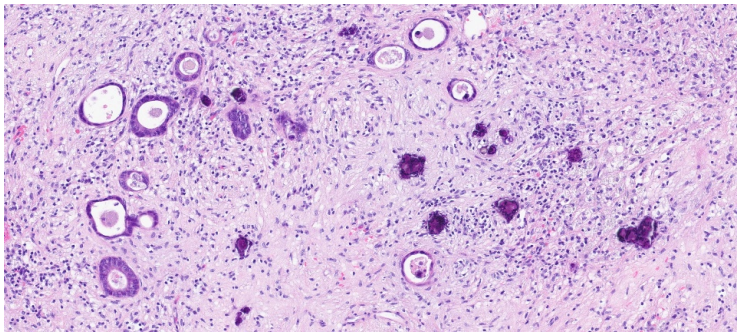


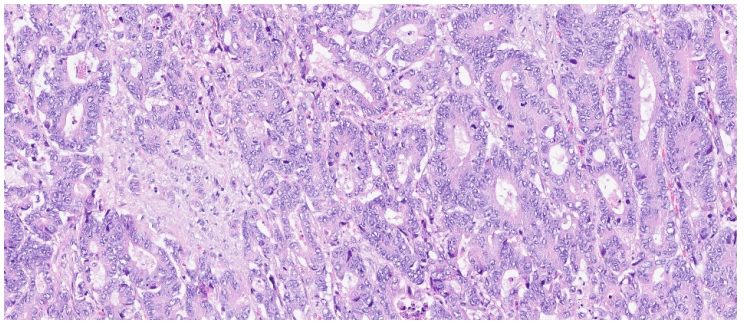
- ✓Patterns of pathological tumor response to chemotherapy
  - ✓Standard against which pathological scores of tumor response and new criteria for radiological response are based
  - ✓Element which may guide surgery
- ✓Degree of pathological tumoral response to chemotherapy
  - ✓Surrogate marker of chemotherapy efficiency
  - ✓Surrogate marker of biological behavior of tumor, recurrence or survival outcomes
  - ✓Integrated as one of endpoints in clinical trial
- ✓Drawbacks related to chemotherapy
  - ✓Chemotherapy associated liver injury (CALI)
  - ✓Poor location of residual cancer cells in HCRM after chemotherapy
  - ✓Missing metastasis on postchemotherapy imaging
  - ✓Decrease accuracy of metastasis detection on postchemott imaging

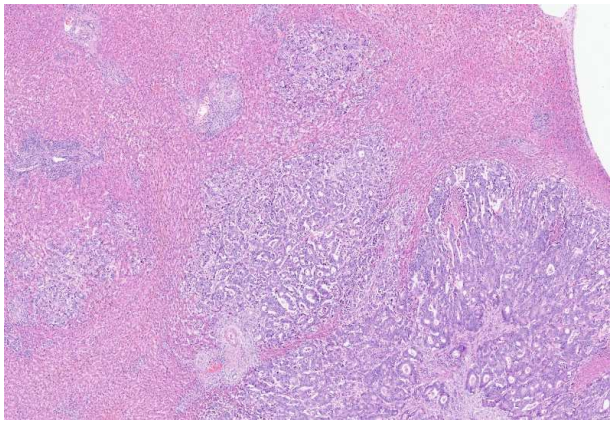
Multiples metastases en réponse partielle (TRG3) ou complete (TRG1)











Foie droit : 13 métastases d'adénocarcinome colorectal moyennement différencié:

- Signes de régression partielle à la thérapie néo-adjuvante (TRG 3).
- Présence de micro-métastases satellite et ront d'invasion présentant un mode de croissance de type remplacement type 2.
- Une englobe la paroi de la veine sus-hépatique moyenne qu'elle infiltre sur toute l'épaisseur et arrive au contact de l'intima. Au contact de l'adventice de la veine sus-hépatique droite. Infiltration de la marge de résection para-veineuse comprise entre les deux veines (R1 vasc).
- Les autres avec marge de résection chirurgicale à une distance

Foie gauche : 3 Métastases d'adénocarcinome du gros intestin moyennement différencié,

- Idem

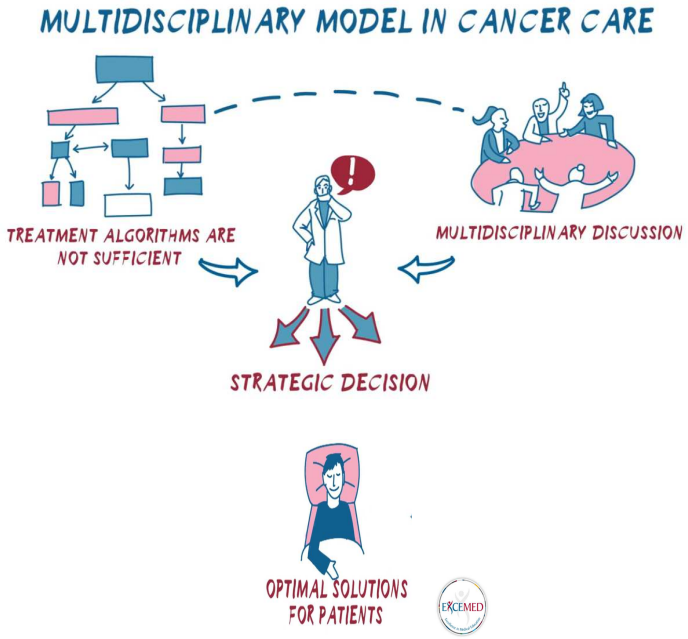
Foie non tumoral :

- minime stéatose macro-vacuolaire 5% des hépatocytes et absence de fibrose.
- Présence de dépôts matériel d'embolisation avec réaction fibro-inflammatoire de type granulomateuse gigantocellulaire à corps étrangers.

Histoire du patient

- Résection antérieure haute (recto-sigmoidienne)
- T2 N1 (2/22) R0
- Surveillance
- ☺

Conclusion: Standard of care in oncology: Multi-Disciplinary Team (MDT) significantly improved survival of advanced CR



- ✓ Improved surgical techniques and strategies
- ✓ Interventional radiology
- ✓ Efficient oncologic drugs
- ✓ Standardized pathology evaluation and molecular biology

Thank you!

Synchronous liver metastasis: systemic disease

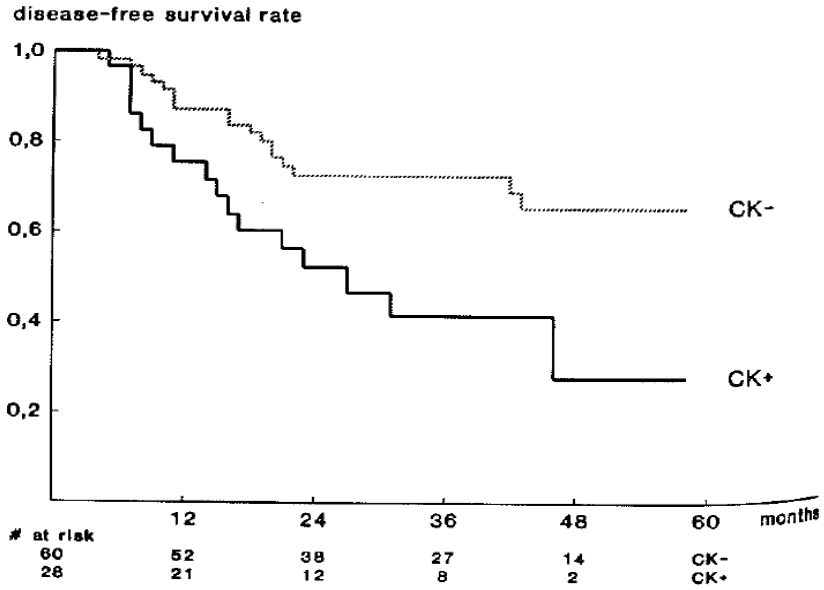
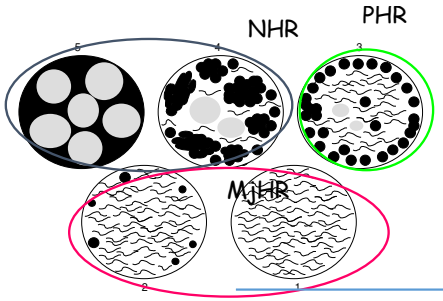


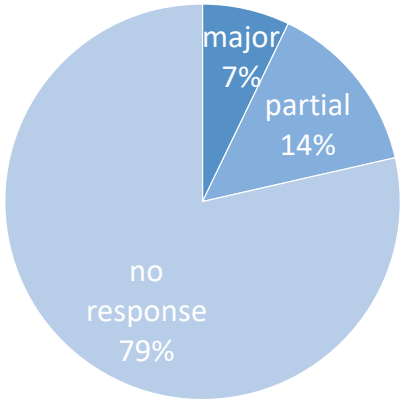
Fig 1—Cumulative disease-free survival rate in patients with (CK+) and without (CK−) bone marrow tumour cells.

Lindenmann F et al, The Lancet 1992

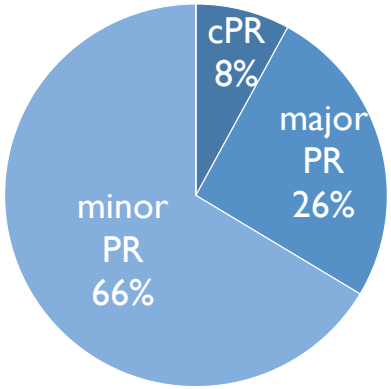


Pathological response depends of type of regimen

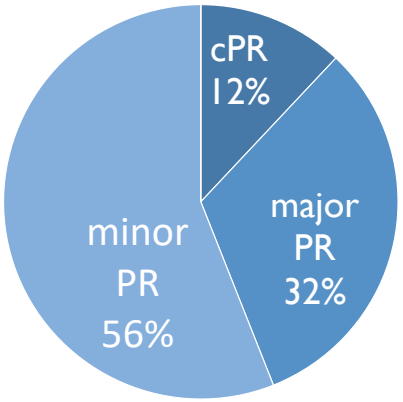
5-FU



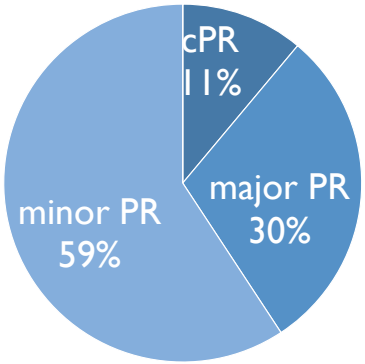
irinotecan



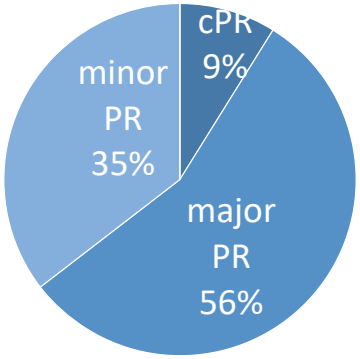
oxaliplatin



iri+bevacizumab



ox+bevacizumab



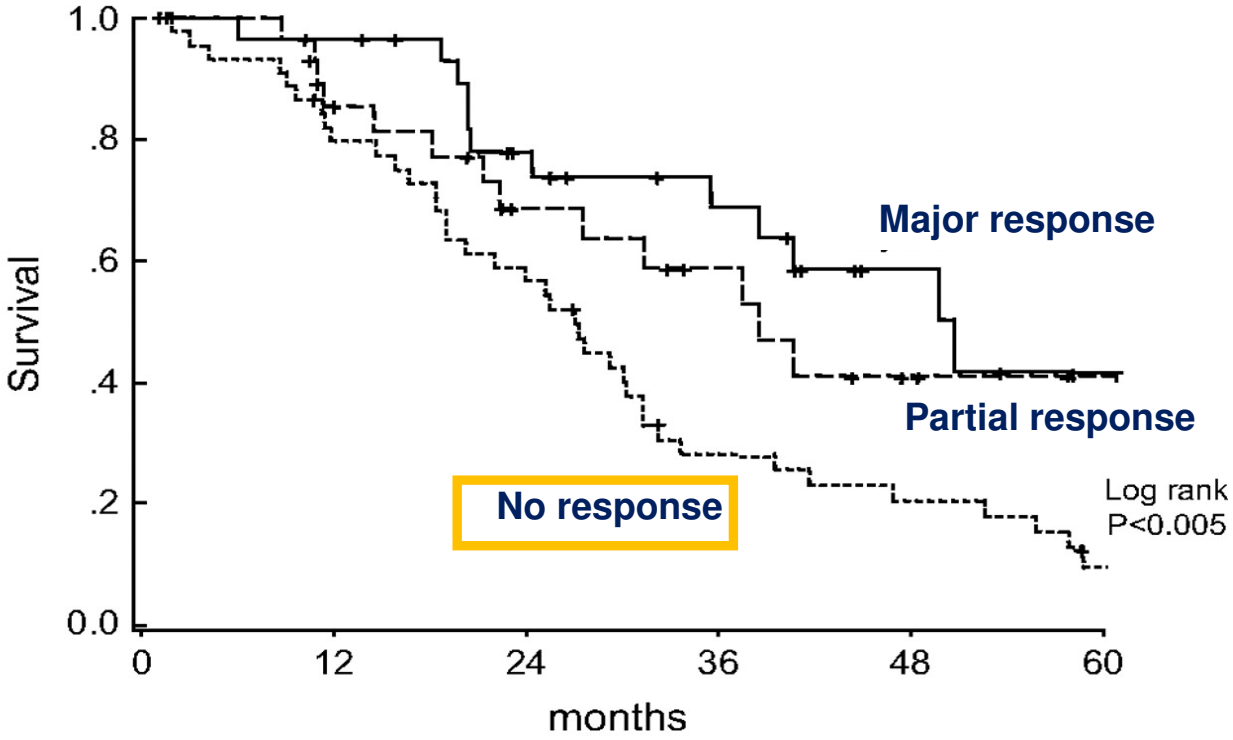
More efficient chemotherapy: complete response

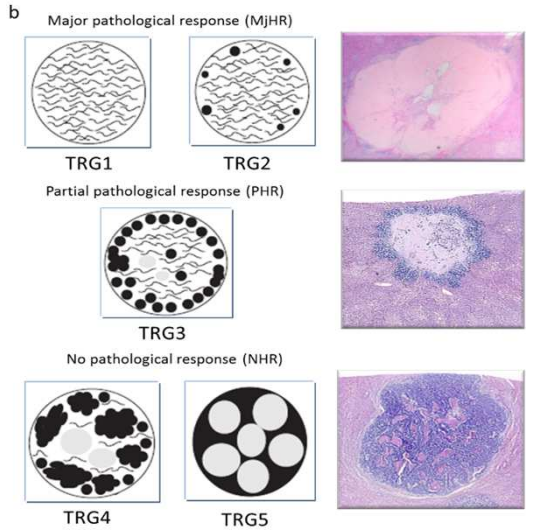
10-15 % of patients

5 year survival: 75%

Mentha G, Sem Liver Dis 2013

Response to chemotherapy predicts survival after surgery





Pathological response after neo-adjuvant chemotherapy

Rubbia-Brandt et al., Ann Oncol 2007