

Metastatic Spread Emerging from Liver Metastases of Colorectal Cancer

Does the Seed Leave the Soil Again?

Nuh N. Rahbari, MD,* Ulrich Bork, MD,* Sebastian Schölch, MD,* Christoph Reissfelder, MD,*
Kristian Thorlund, PhD,† Alexander Betzler, MD,* Christoph Kahlert, MD,‡ Martin Schneider, MD,‡
Alexis B. Ulrich, MD,‡ Markus W. Büchler, MD,‡ Jürgen Weitz, MD,* and Moritz Koch, MD*

Ann Surg. 2016 Feb;263

ILS ONT ESSAYÉ DE NOUS ENTERRER.

**ILS NE SAVAIENT PAS
QUE NOUS ÉTIONS DES GRAINES.**

-Proverbe mexicain-

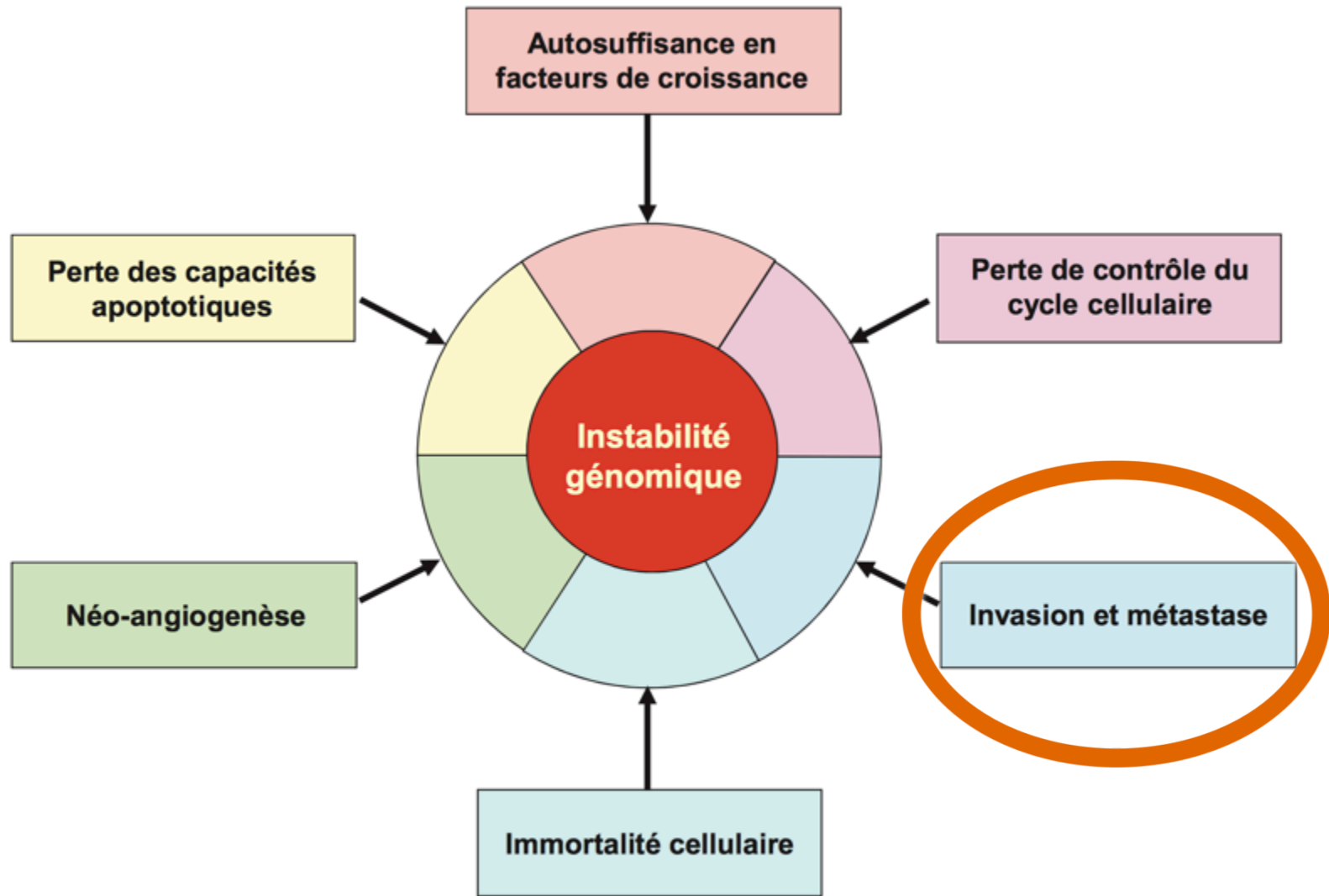
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Plan

- Généralités: la cascade métastatique et les cellules tumorales circulantes
- Article
 - Matériel et méthode
 - Résultats
- Discussion et revue de la littérature
- Conclusion



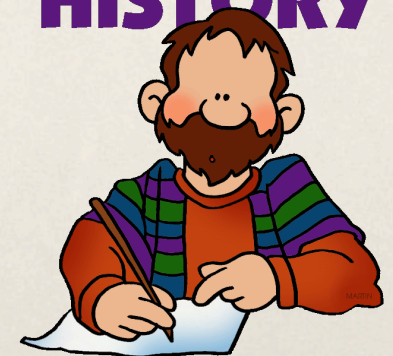


Hanahan & Weinberg, *Cell* 2000; 100: 57-70

Comment et pourquoi une cellule métastase?

- 1889: PAGET: seed and soil hypothesis
- 1928: EWING: colonisation d'organes fortement vascularisés
- 2eme partie du XXème s: sélection clonale
- 2002: BERNARDS et WEINBERG la signature métastatique pré-déterminées: signature moléculaire tumorale
 - Weinberg RA. A progression puzzle. Nature 2002

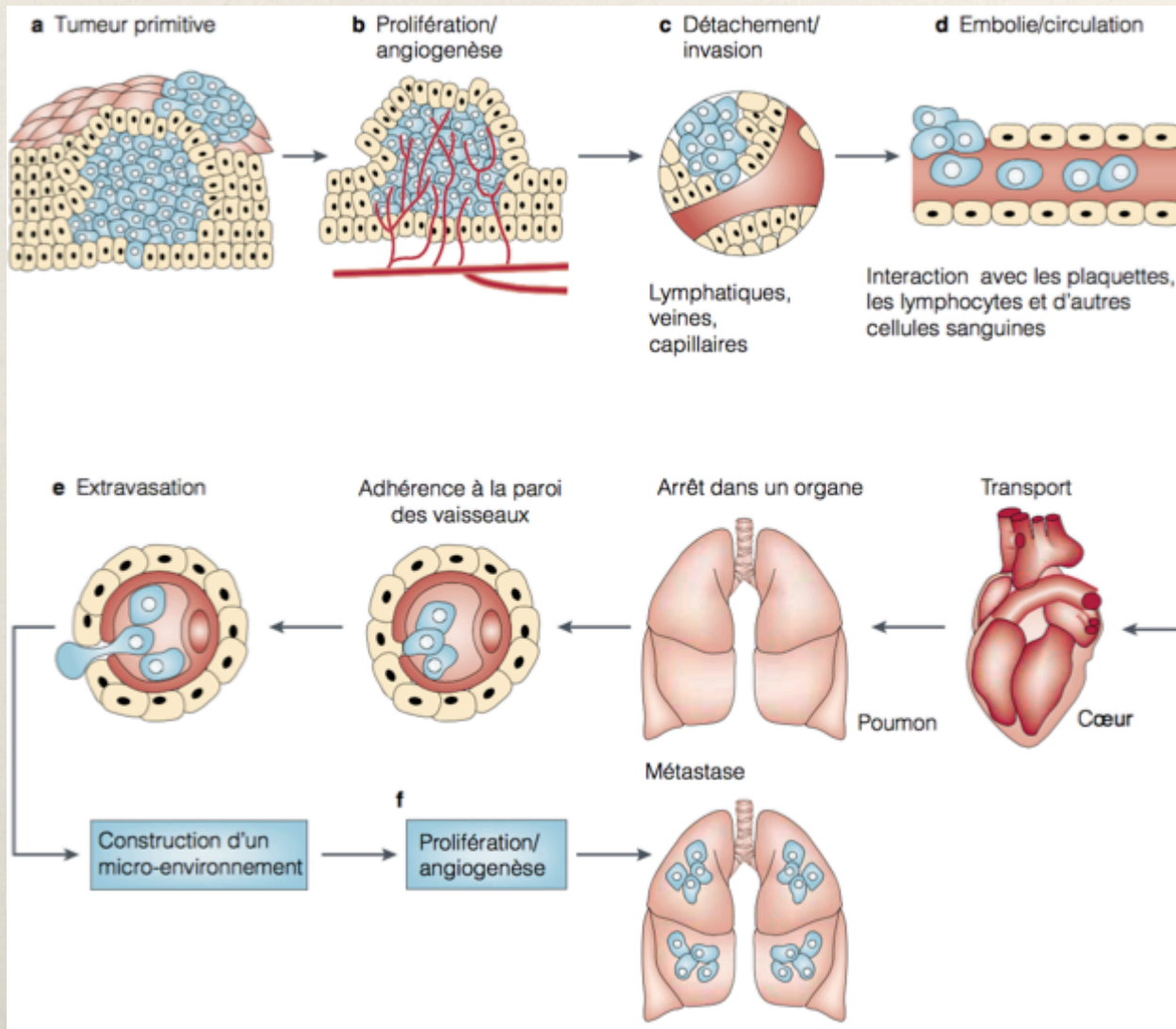
HISTORY



La cascade métastatique

- **Mécanismes et concepts multiples:**
 - Angiogénèse et switch angiogénique
 - Lymphangiogénèse
 - Perte de l'adhésion cellulaire
 - Transition épithélio-mésenchymateuse
 - Niches métastatiques
 - Accroche sur le site secondaire
 - Notion cellules dormantes
 - Micro-environnement
 - Signature moléculaire et gènes de métastases

La cascade métastatique





Stephen Paget (1855-1926)

THE LANCET.

Volume 133, 23 mars 1889

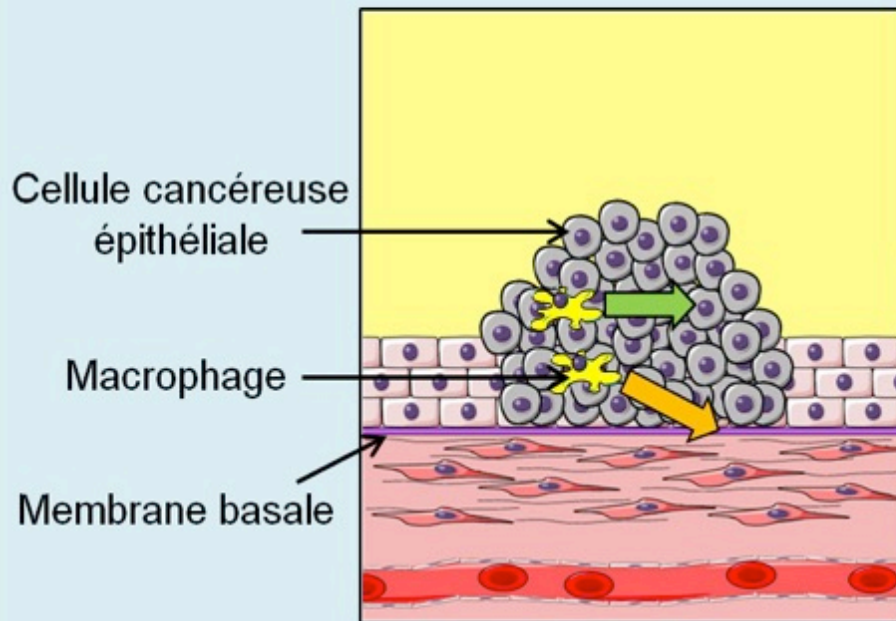
THE
DISTRIBUTION OF SECONDARY GROWTHS
IN CANCER OF THE BREAST.
BY STEPHEN PAGET, F.R.C.S.,
ASSISTANT SURGEON TO THE WEST LONDON HOSPITAL AND THE
METROPOLITAN HOSPITAL.

The "seed and soil"
theory of metastasis
=

Concept de niche
prémétastatique

Concept de mobilité cellulaire et transition épithélio-mésenchymateuse

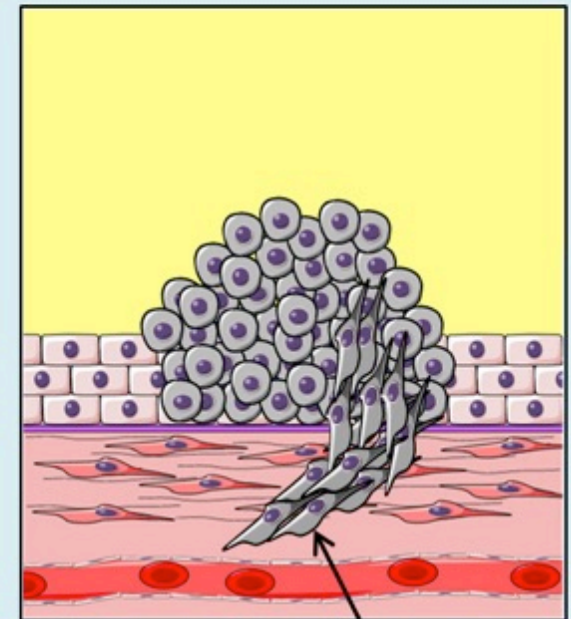
Carcinome in situ



Invasion



Carcinome invasif

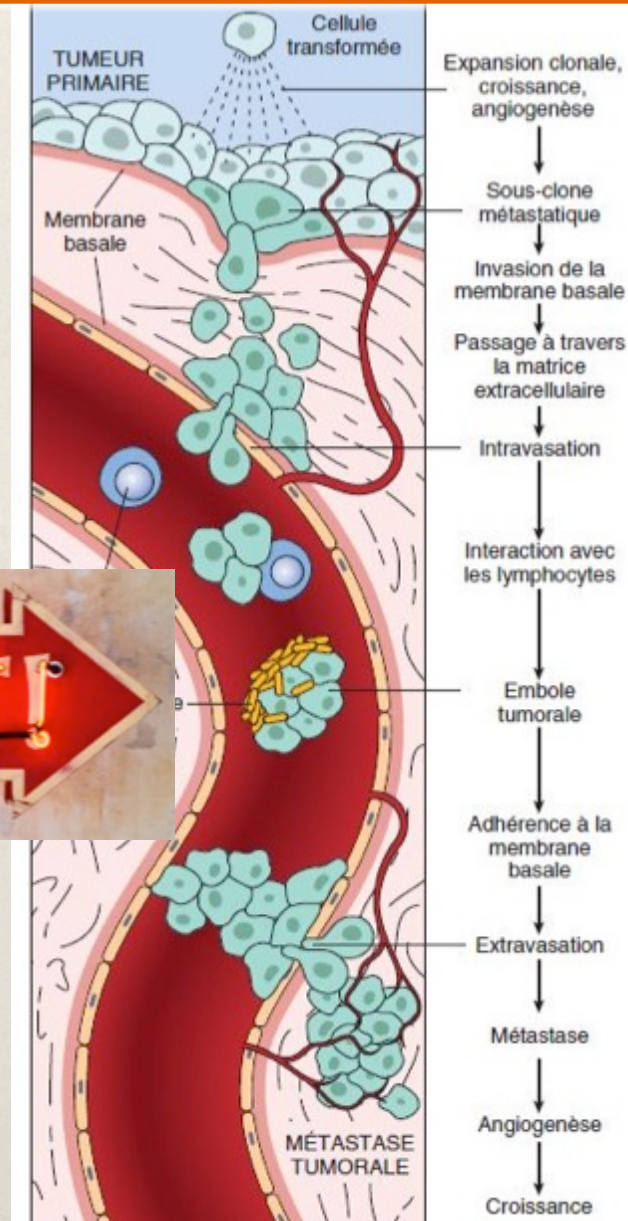


➡ $\text{TGF}\beta$ = EMT

➡ MMP = Dégradation membrane basale

Cellule cancéreuse
mésenchymateuse

Les cellules tumorales circulantes



THIS IS IT!

« Self-seeding » et dissémination asynchrone

Tumor Self-Seeding by Circulating Cancer Cells

KIM al. Memorial Sloan-Kettering Cancer Center,

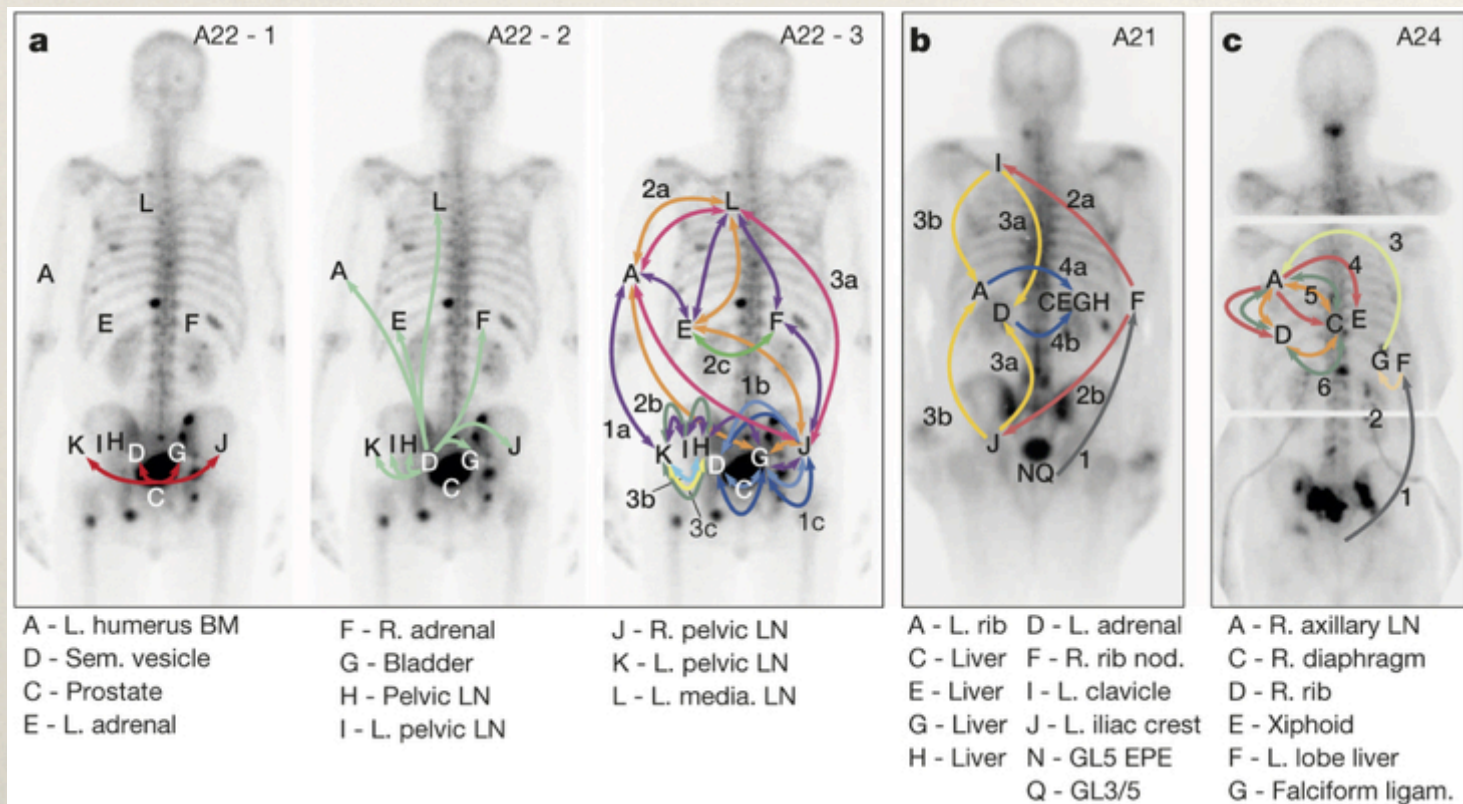


Clinical implications of cancer self-seeding.
Elizabeth Comen, Larry Norton & Joan Massagué
Nature Reviews Clinical Oncology **8**, 369-377 (June 2011)



La métastase de la métastase

Does the seed leave the soil again ?



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Février 2016 ; numero 263



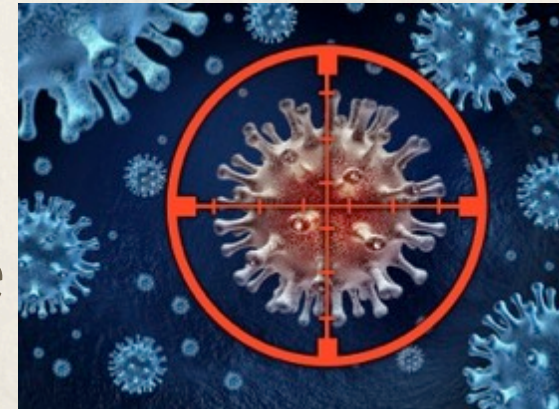
Méthode

- Etude de recherche clinique « fondamentale », observationnelle
- Prospective: octobre 2010- février 2015
- multicentrique

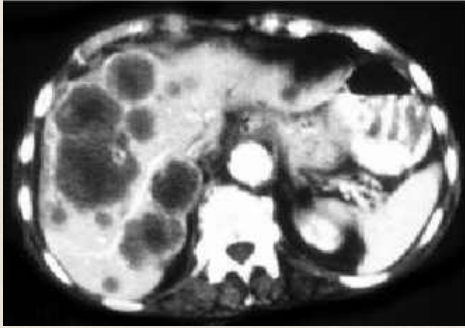


Objectifs

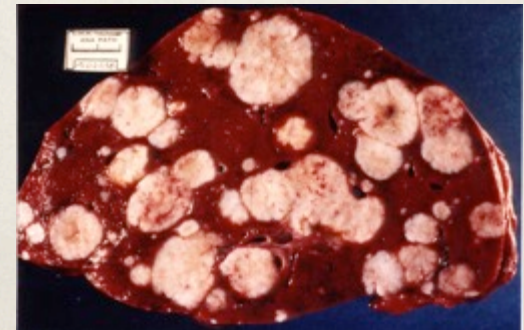
- Détection des cellules tumorales circulantes dans le cancer colo-rectal métastatique hépatique
 - En pré et post-hépatique
- Etude du potentiel métastatique
 - Phénotypage et génotypage



Population étudiée

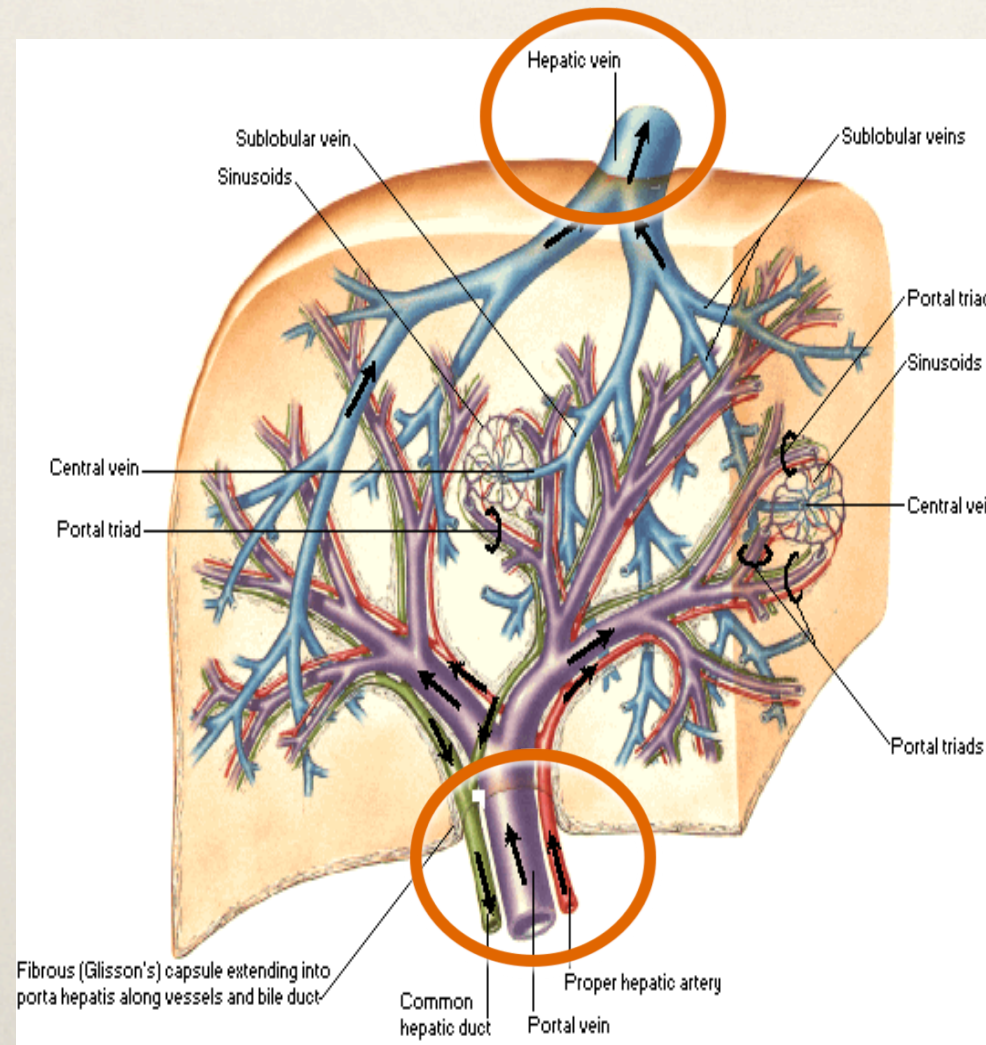


- Patients avec résection chirurgicale de métastases hépatiques de cancer colo-rectal
- 2 groupes:
 - Groupe d'essai et de validation
- Critères d'exclusion:
 - Antécédent autre tumoral, absence de métastase à l'anapath de la pièce

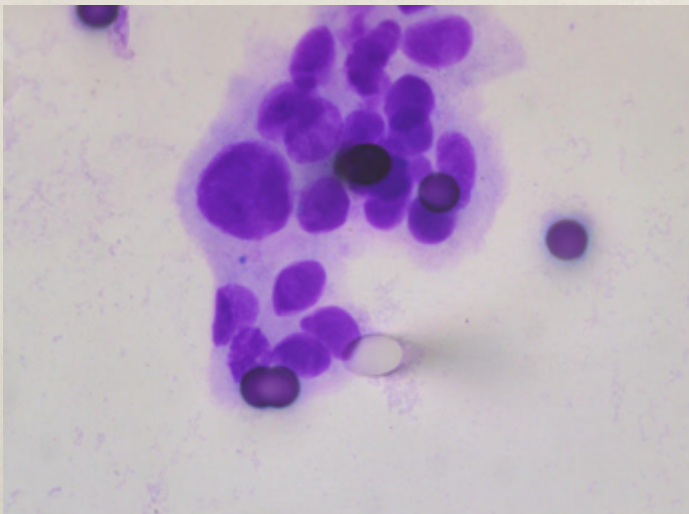


Méthodes: prélèvements

- Prélèvements veineux:
 - Veine portale : PVB
 - Veine sus-hépatique: HVB
 - Artère radiale
- Avant toute mobilisation hépatique



Méthodes: isolation CTCs

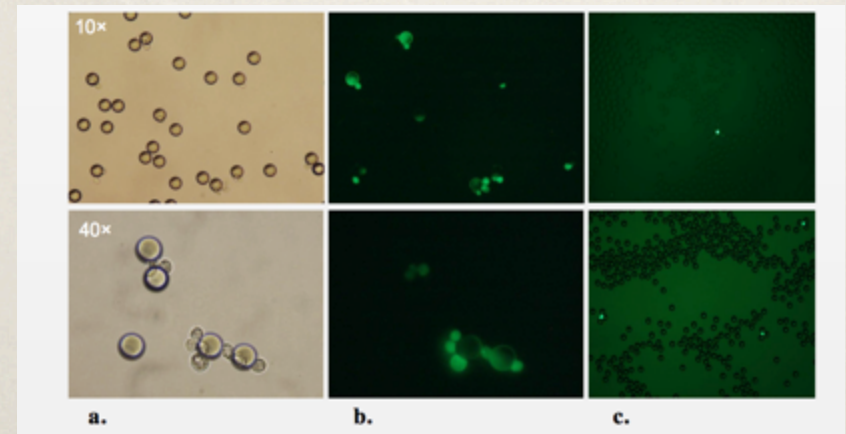
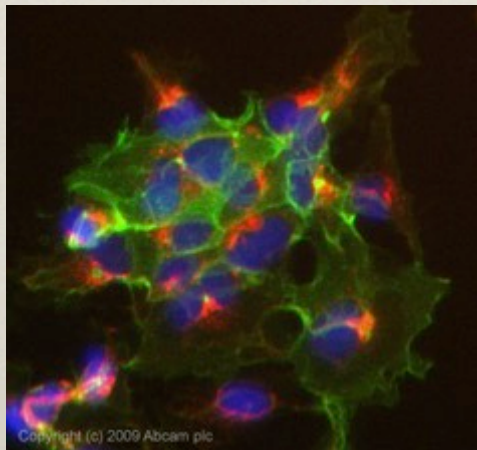
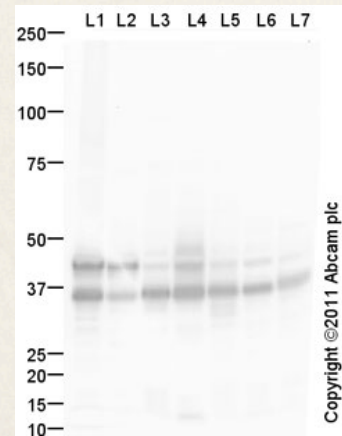


Seuils de détections

- ≥ 2 CTCs : seuil habituel retenu dans les différentes études
- 2 autres seuils:
 - ≥ 1 CTCs
 - ≥ 3 CTCs
 - Objectifs: augmenter la précision et la sensibilité de leurs résultats

Analyse phénotypique et génotypique

- Des CTCs
- Des cellules des métastases hépatiques
- Immunohistochimie: EpCAM antibody
- Extraction ARN/rt-PCR



Résultats: la population

TABLE 1. Clinicopathologic Characteristics of the Training and Validation Sets

	Training Set		Validation Set	
	All Patients	Primary Removed	All Patients	Primary Removed
n	55 (100)	37 (100)	50 (100)	40 (100)
Sex				
Male	31 (56.4)	22 (59.5)	34 (68.0)	28 (70.0)
Female	24 (43.6)	15 (40.5)	16 (32.0)	12 (30.0)
Age (years)	61 (34–84)	61 (34–74)	64 (41–77)	66 (41–77)
Disease-free interval (months)	0 (0–123)	4 (0–123)	0 (0–55)	1 (0–55)
Initial stage of disease (UICC)				
III	3 (5.4)	3 (8.1)	4 (8.0)	4 (10.0)
IV	52 (94.6)	34 (91.9)	46 (92.0)	36 (90.0)
Node-positive primary				
Yes	33 (61.1)	22 (61.1)	34 (70.8)	26 (65.0)
No	21 (38.9)	14 (38.9)	14 (29.2)	14 (35.0)
Site of primary tumor				
Colon	36 (65.5)	26 (70.3)	36 (72.0)	30 (75.0)
Rectum	19 (34.5)	11 (29.7)	14 (28.0)	10 (25.0)
Previous resection of primary				
Yes	37 (67.3)	37 (100)	40 (80.0)	–
No	18 (32.7)	–	10 (20.0)	20 (100)
Number of metastases				
1	25 (45.5)	17 (45.9)	20 (40.0)	14 (35.0)
>1	30 (54.5)	20 (54.1)	30 (60.0)	26 (65.0)
Size of largest metastasis (cm)				
<5	41 (74.5)	29 (78.4)	40 (80.0)	32 (80.0)
≥5	14 (25.5)	8 (21.6)	10 (20.0)	8 (20.0)
Distribution of metastases				
Unilobar	44 (80.0)	32 (86.5)	32 (64.0)	25 (62.5)
Bilobar	11 (20.0)	5 (13.5)	18 (36.0)	15 (37.5)
Extrahepatic disease				
Yes	9 (16.4)	7 (18.9)	16 (32.0)	10 (25.0)
No	46 (83.6)	30 (81.1)	34 (68.0)	30 (75.0)
CEA level (μg/L)	4.5 (0.3–1338)	3.9 (0.3–51.1)	5.1 (0.4–1023.6)	5.6 (0.4–542)
CA 19–9 level (μg/L)	15.6 (1–5276)	13.7 (1–473.6)	20.6 (2–26,676.2)	18.4 (2–5661.4)
MSKCC risk score				
≤2	33 (60.0)	25 (67.6)	33 (66.0)	27 (67.5)
>2	22 (40.0)	12 (32.4)	17 (34.0)	13 (32.5)
Neoadjuvant therapy				
Yes	18 (34.6)	15 (40.5)	24 (48.0)	20 (50.0)
No	34 (65.4)	22 (59.5)	26 (52.0)	20 (50.0)

Data are presented as n (%) or median (range).

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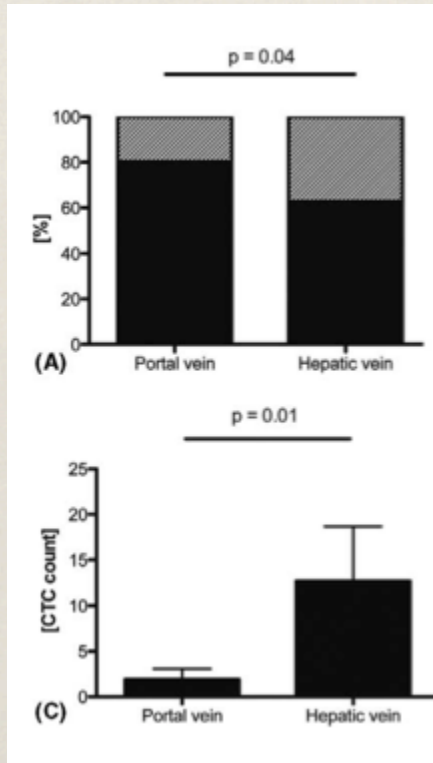
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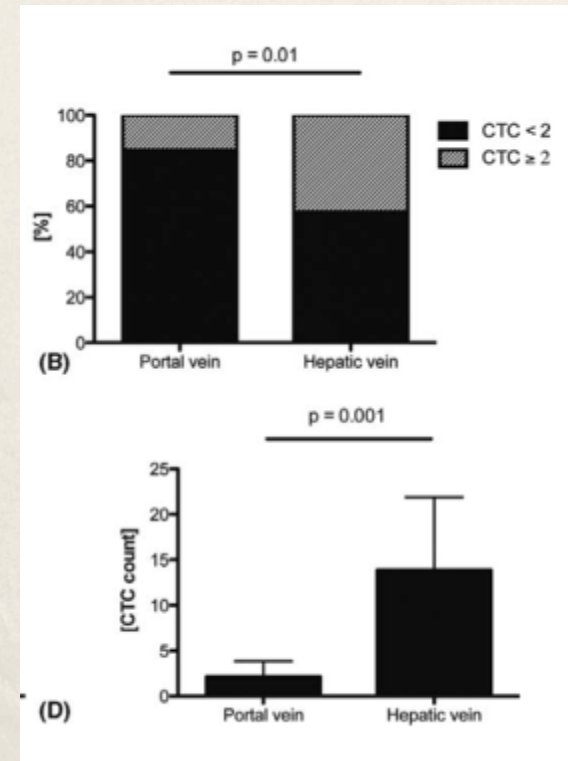
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Détection et compte des CTCs



Cohorte complète avec
ou sans primitif en
place



Sous groupe sans
primitif en place

Détection et compte des CTCs

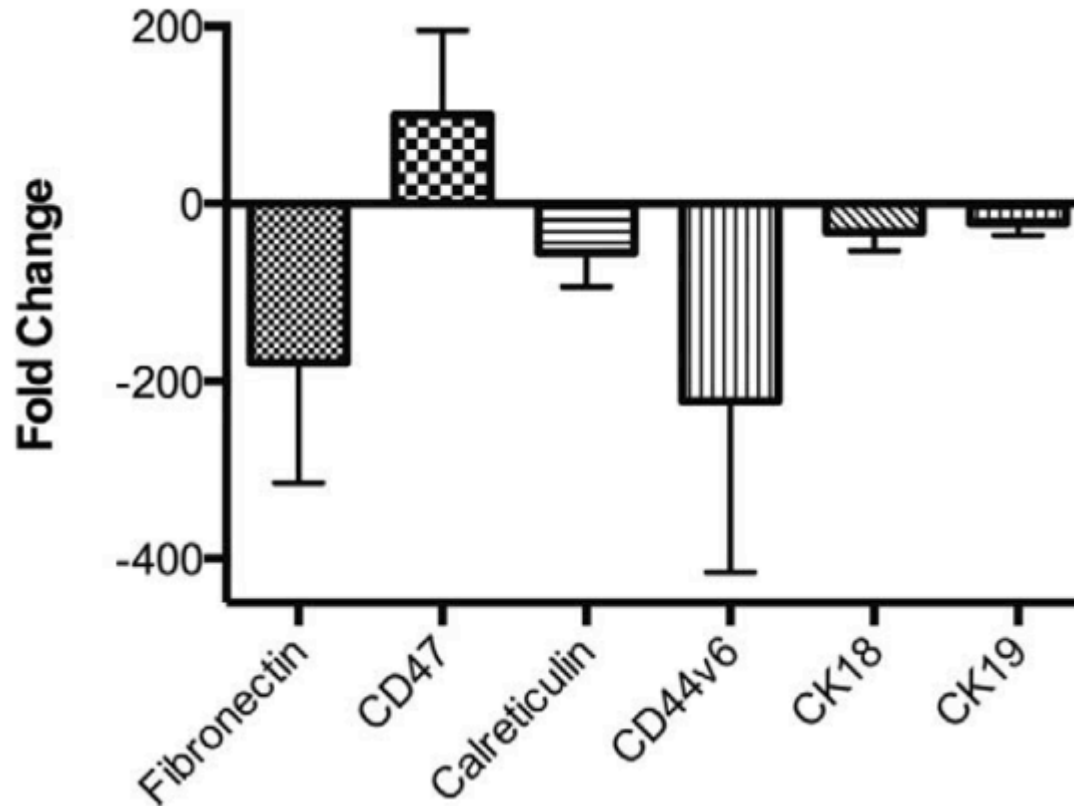
p 0,05	primitif en place	sans primitif en place
Taux de détection HVB	38,2 %	42,4 %
Taux de détection PVB	19,6 %	15,2%
CTC HVB	11,9 +/- 5,5	13,9+/-8,0
CTC PVB	1,9 +/- 1,2	2,1+/-1,8

CTC sup ou égal à 2

Détection et compte des CTCs

**EN FAVEUR D'UNE
PROBABLE ACTIVITE
MÉTASTATIQUE DES
MÉTASTASES HÉPATIQUES**

Phénotype des CTCs



Fibronectine/ CD44v6: adhésion cellulaire

Calreticuline: pro-phagocytaire, CD47: anti-phagocytaire

CK19/CK18: marqueurs épithéliaux

Phénotype des CTCs

**PHÉNOTYPE INVASIF:
TRANSITION EPITHELIO-
MESENCHYMATEUSE
ET
DIFFUSION METASTATIQUE**



Des CTCs, oui!

Mais, chez qui?

TABLE 4. Multivariate Analyses of Factors Associated with Tumor Cell Detection in the Hepatic Vein Compartment

Variable	Comparison	Odds Ratio	95% CI	<i>P</i>
Training set				
All patients				
Size of largest metastasis (cm)	≥5 vs <5	5.1	1.1–25.1	0.04
CEA (μg/L)	≥4.4 vs <4.4	5.4	1.2–24.3	0.02
Primary tumor removed				
Size of largest metastasis (cm)	≥5 vs <5	—	—	—
CEA (μg/L)	≥4.4 vs <4.4	5.3	1.0–30.6	0.05
Validation set				
All patients				
Sex	Male vs female	0.2	0.1–1.7	0.16
Size of largest metastasis (cm)	≥5 vs <5	—	—	—
CEA (μg/L)	≥4.4 vs <4.4	1.5	0.2–9.3	0.69
CA19–9 (μg/L)	≥24.9 vs <24.9	9.3	1.5–59.5	0.02
Primary tumor removed				
Age (yrs)	≥65 vs <65	0.4	0.1–2.9	0.36
Size of largest metastasis (cm)	≥5 vs <5	—	—	—
CEA (μg/L)	≥4.4 vs <4.4	0.6	0.1–5.7	0.7
CA19–9 (μg/L)	≥24.9 vs <24.9	9.2	1.1–79.7	0.04

Multivariate analysis was not feasible for the size of largest metastases in patients with previous resection of the primary tumor due to the lack of events for the combination of patients with metastases ≥5 cm and without detectable CTCs in the hepatic vein.

CEA indicates carcinoembryonic antigen.

En somme

- Présence de CTCs chez les patients présentant des métastases hépatiques d'origine colo-rectales
- Relarguées directement par ces métastases
- Tumeur primitive en place ou non
- FR:
 - Taille métastase > 5 cm
 - ACE > 4,4; CA 19.9 > 24,9 : pour 2 CTCs

L'hypothèse de la métastase de la métastase semble donc être une réalité

L'envie du repas ne fait pas manger l'écuelle

Proverbe Touareg

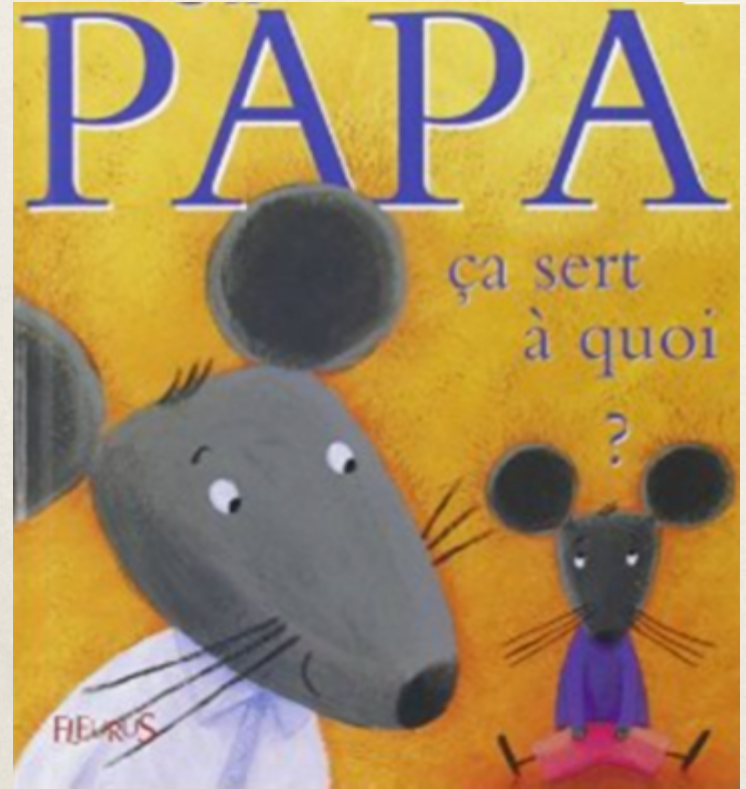
Des questions?

- Quelles implications?
- Quelle valeur pronostic?
- Guide des traitements et des décisions thérapeutiques?
- Possibilité de recherche?
- Et toutes les vôtres... 😊



Implications des CTCs dans le CCR?

- En adjuvant
- En situation métastatique



CTCs dans le CCR en adjuvant

- En per-opératoire: relargage de CTCs et hypothèses du no-touch
- Meilleur pronostic si baisse rapide des CTCs en post-opératoire ou après radio-chimiothérapie pour rectum
 - *Clearance of circulating tumor cells after excision of primary colorectal cancer. Ann Surg 2002 Patel H*
 - *Decreased detection rate of disseminated tumor cells of rectal cancer patients after preoperative chemoradiation: a first step towards a molecular surrogate marker for neoadjuvant treatment in colorectal cancer. Ann Surg 2003, Kienle P*

Situation adjuvante

- **Impact pronostic à long terme:**
 - *Does the presence of circulating tumor cells in the venous drainage of curative colorectal cancer resections determine prognosis? A meta-analysis. Ann Surg Oncol 2008, Katsuno H*
 - **20% N+ si CTCs- vs 50% N+ si CTCs +**
 - *Meta-analysis shows that detection of circulating tumor cells indicates poor prognosis in patients with colorectal cancer. Gastroenterology 2010, Rahbari*
 - **risque N+ , DFS et métastases quelques soit le stade tumoral (I, II ou III)**

Stade 0	pTis N0 M0
Stade I	pT1-2 N0 M0
Stade IIA	pT3 N0 M0
Stade IIB	pT4a N0 M0
Stade IIC	pT4b N0 M0
Stade IIIA	pT1-T2 N1/N1c M0 et pT1 N2a M0
Stade IIIB	pT3-T4a N1N1cM0, pT2 T3N2aM0, pT1 T2N2bM0
Stade IIIC	p T4a N2a M0; p T3,T4a N2b M0; pT4b N1-N2M0
Stade IVA	tout T, Tout N, M1a
Stade IVB	tout T, tout N, M1b

Situation métastatique

Reference	Patients	CTC detection rate (threshold)	Clinical significance
Allard, 2004 [10]	N=196 Stage IV	Stage IV: 30% Threshold $\geq 2\text{CTC}/7.5\text{ml}$	N/A
Cohen, 2006 [134]	N=50 Stage IV	Stage IV: 38% Threshold $\geq 2\text{CTC}/7.5\text{ml}$	- CTC positivity was associated with disease status (progression vs. non-progression).
Sastre, 2008 [135] Maestro 2009	N= 94 Stage I–IV	Stage II: 21% Stage III: 24% Stage IV: 61%	
Cohen 2008 [105] Cohen 2009 [137]	N=430 Stage IV	Stage IV: 33% before treatment 12% at week 3-5 Threshold $\geq 3\text{CTC}/7.5\text{ml}$	- CTC positivity at baseline was independently associated with worse PFS (5 vs. 8 months) and OS (9 vs. 18 months). - Among initially CTC positive patients, those who become CTC negative at weeks 3–5 had a better PFS (6 vs. 2 months).
Hiraiwa 2008 [32]	N=40	Stage III: 10% Stage IV: 41% Threshold $\geq 2\text{CTC}/7.5\text{ml}$	- CTC positivity was not associated with outcome in the 29 stage-IV patients
Jiao 2009 [102]	N=29, with surgically resected liver metastases	N/A 7.5ml of blood analyzed at different sites (peripheral, portal and hepatic veins)	- Surgical resection immediately reduced the number of CTCs compared with radiofrequency ablation, which was associated with an increased number of CTCs
Tol 2010 [106]	N=467	Stage IV: 29% before treatment 5% at week 3-5 Threshold $\geq 3\text{CTC}/7.5\text{ml}$	- CTC positivity at baseline was associated with worse PFS (8 vs. 10.5 months) and OS (14 vs. 22 months). - Among initially positive patients, those who became CTC negative at weeks 1–2 had a better PFS (8 vs. 4 months)
Papavasiliou 2010 [138]	N=20, with surgically resected liver metastases	Preoperative: 100% Peroperative: 50% Postoperative: 5% Threshold $\geq 3\text{CTC}/30\text{ml}$	Postoperative CTC detection was associated with DMFS and OS.

Relationship of circulating tumor cells to tumor response, progression-free survival, and overall survival in patients with metastatic colorectal cancer.

Cohen SJ¹, Punt CJ, Iannotti N, Saidman BH, Sabbath KD, Gabrail NY, Picus J, Morse M, Mitchell E, Miller MC, Doyle GV, Tissing H, Terstappen LW, Meropol NJ.

Purpose

As treatment options expand for metastatic colorectal cancer (mCRC), a blood marker with a prognostic and predictive role could guide treatment. We tested the hypothesis that circulating tumor cells (CTCs) could predict clinical outcome in patients with mCRC.

Patients and Methods

In a prospective multicenter study, CTCs were enumerated in the peripheral blood of 430 patients with mCRC at baseline and after starting first-, second-, or third-line therapy. CTCs were measured using an immunomagnetic separation technique.

Results

Patients were stratified into unfavorable and favorable prognostic groups based on CTC levels of three or more or less than three CTCs/7.5 mL, respectively. Patients with unfavorable compared with favorable baseline CTCs had shorter median progression-free survival (PFS; 4.5 v 7.9 months; $P = .0002$) and overall survival (OS; 9.4 v 18.5 months; $P < .0001$). Differences persisted at 1 to 2, 3 to 5, 6 to 12, and 13 to 20 weeks after therapy. Conversion of baseline unfavorable CTCs to favorable at 3 to 5 weeks was associated with significantly longer PFS and OS compared with patients with unfavorable CTCs at both time points (PFS, 6.2 v 1.6 months; $P = .02$; OS, 11.0 v 3.7 months; $P = .0002$). Among nonprogressing patients, favorable compared with unfavorable CTCs within 1 month of imaging was associated with longer survival (18.8 v 7.1 months; $P < .0001$). Baseline and follow-up CTC levels remained strong predictors of PFS and OS after adjustment for clinically significant factors.

Conclusion

The number of CTCs before and during treatment is an independent predictor of PFS and OS in patients with metastatic colorectal cancer. CTCs provide prognostic information in addition to that of imaging studies.

Quel pronostic si métastases

Circulating Tumor Cells and Prognosis of Patients with Resectable Colorectal Liver Metastases or Widespread Metastatic Colorectal Cancer: A Meta-Analysis

Bas Groot Koerkamp, MD, PhD¹, Nuh N. Rahbari, MD², Markus W. Büchler, MD², Moritz Koch, MD², and Jürgen Weitz, MD²

Annals of

SURGICAL ONCOLOGY

OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

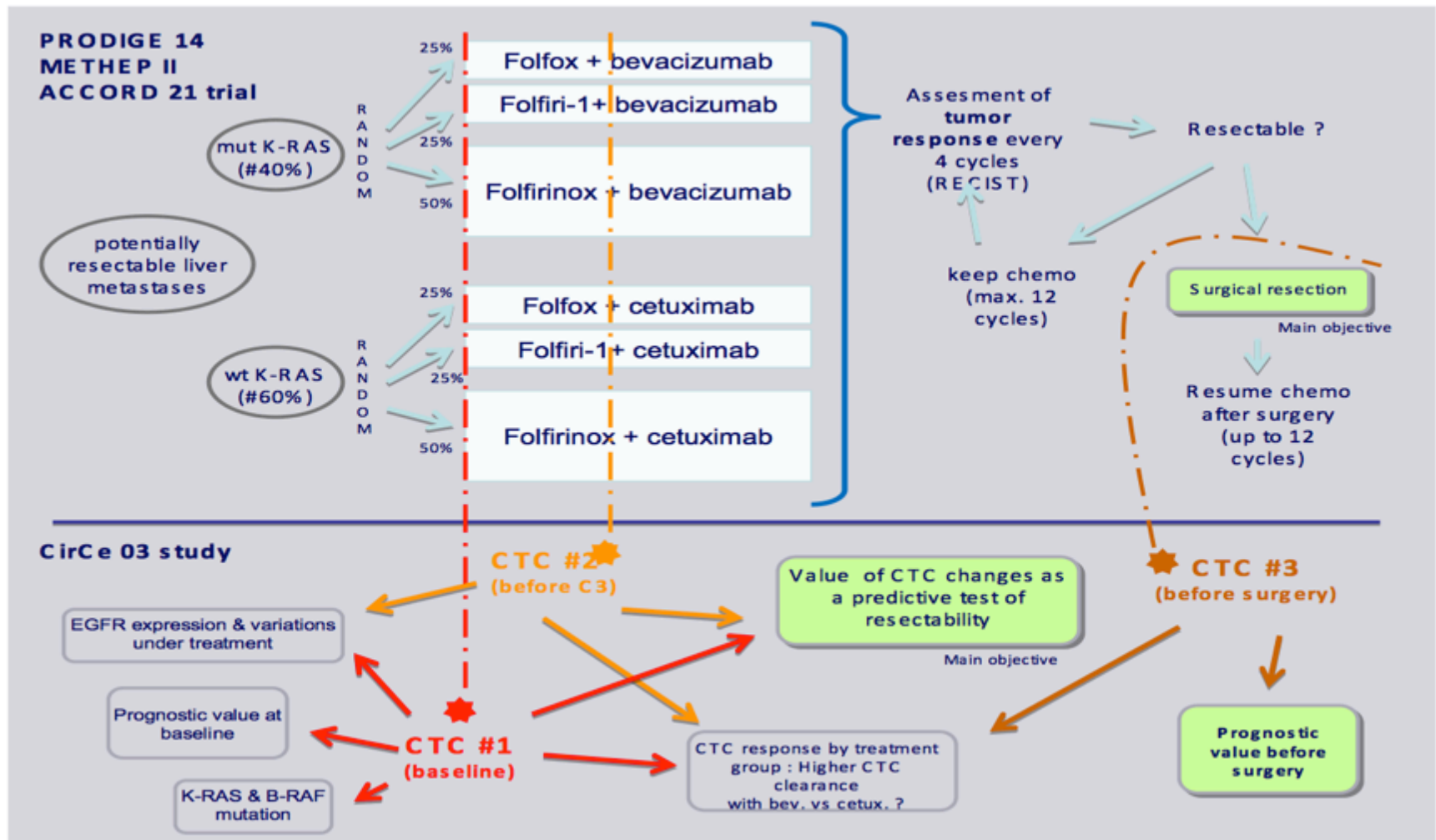
2013

Results. The literature search yielded 16 studies representing 1,491 patients. The results of 12 studies representing 1,329 patients were suitable for pooled analysis. The overall survival (HR, 2.47; 95 % CI 1.74–3.51) and progression-free survival (PFS) (HR, 2.07; 95 % CI 1.44–2.98) were worse in patients with CTCs. The subgroup of studies with more than 35 % CTC-positive patients was the only subgroup with a statistically significant worse PFS. All eight studies that performed multivariable analysis identified the detection of CTCs as an independent prognostic factor for survival.



Un guide pour la chirurgie ?

Etude ancillaire CirCe 03



D'autres bio-marqueurs

- * disseminated tumor cells (DTC): issues de la moelle osseuse
- * ADN circulant
- * miARN

Les CTCs, optiques de recherche futur

- Optique quantitative: comparaison entre CTCs et nouveaux biomarqueurs
- Optique qualitative: **BIOPSIE LIQUIDE** (*ex:EGFR*)
 - choix du traitement initial, intégration dans les TNM i+
 - au décours du suivi: efficacité du traitement, acquisition de résistance à la chimiothérapie, guide pour thérapie ciblée, pour immunothérapie
 - Sans nécessité de biopsie invasive

Comparative analysis of innate immune system function in metastatic breast, colorectal, and prostate cancer patients with circulating tumor cells

Mark F. Santos^{a,*}, Venkat K.R. Mannam^a, Barbara S. Craft^b, Louis V. Punecky^b, Natale T. Sheehan^b, Robert E. Lewis^a, Julius M. Cruse^a





Critiques article



Validité interne

- Les +:
- Article récent, méthodologie avec groupe contrôle et standard actuel, étude prospective
- Pertinence du critère de jugement
- Population type
- Les -:
- Faible effectif, reproductibilité des analyses
- Manque d'ambition dans leurs analyses

Validité externe

- Les +:
- bases physiopathologiques solides
- application en pratique avec facteur pronostic pour métastases de 5 cm
- Rejoint les articles déjà publiés
- sujet d'actualité avec optiques futures
- Les -:
- Réelle prise de position
- ACE...

Conclusion

- ✱ Les métastases hépatiques peuvent relarguer des CTCs (FR: ACE et taille supérieure à 5 cm)
- ✱ Indépendamment de la présence de la tumeur primitive
- ✱ **facteur pronostic indépendant**
- ✱ Possible facteur de **suivi**, d'**estimation** précoce de la réponse thérapeutique et de **décision**
- ✱ Nombreuses applications possibles futur pour un « **traitement à la carte** »

Fin