CT-DNA dans le cancer colorectal métastatique: quel rôle dans le suivi après les traitements en RIO?

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Ins

HeKA

Faut-il utiliser l’ADN tumoral circulant dans l’ablation des métastases hépatiques de cancer colorectal?

cancers

MDPI

Article

Next-Generation Sequencing Targeted Panel in Routine Care for Metastatic Colon Cancers

Arnaud Bayle [1,†], Debora Basile [1,†], Simon Garinet [2,3], Bastien Rance [4], Pierre Laurent-Puig [2,3], Hélène Blons [2,3], Julien Taieb [1,3,*] and Geraldine Perkins [1,3]

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† A.B. and D.B. contributed to this work equally.

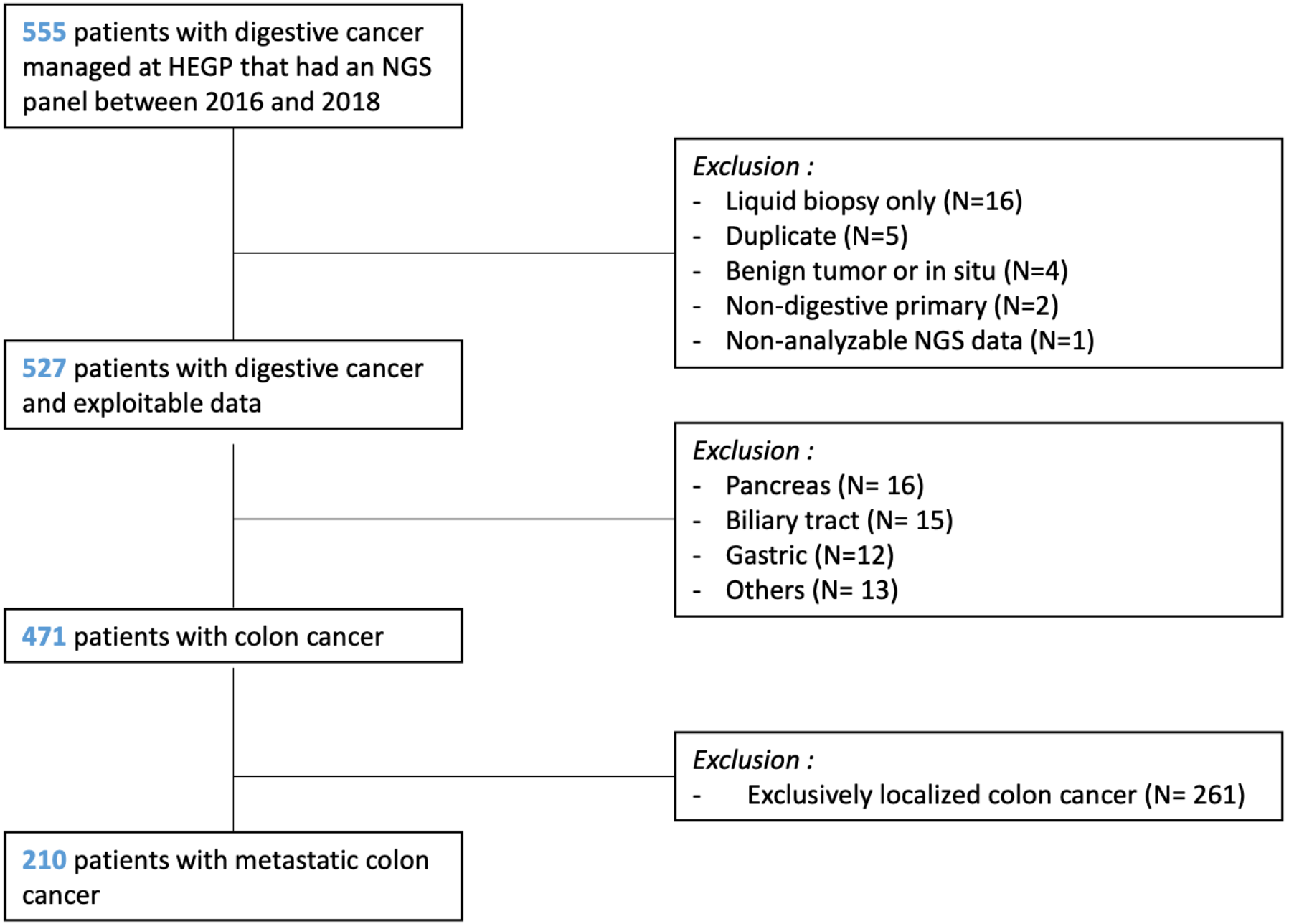


Figure 1. Flowchart.

Corpus ID: 87044013

Les acides nucleiques du plasma sanguin chez l' homme

P. Mandel, P. Métais • Published 2 January 1948 • Biology • Comptes rendus des séances de la Société de biologie et de ses filiales

1948:
Description initiale

[CANCER RESEARCH 37, 646–650, March 1977]

Free DNA in the Serum of Cancer Patients and the Effect of Therapy

S. A. Leon, B. Shapiro, D. M. Sklaroff, and M. J. Yaros

Departments of Nuclear Medicine and Radiation Therapy, Division of Radiology, Albert Einstein Medical Center, Philadelphia, Pennsylvania 19141

1977:
ADN total, biomarqueur

1977

« The source of free DNA in solution in the serum is unknown at present. »

1977

« we conclude that normal serum contains very little free DNA; In cancer patients, higher concentrations of DNA in the serum may be expected »

1977

« Conversely, decrease in DNA levels during treatment seem to be a better prognostic sign »

ARTICLE NAVIGATION

TUMOR BIOLOGY | FEBRUARY 01 2001

DNA Fragments in the Blood Plasma of Cancer Patients: Quantitations and Evidence for Their Origin from Apoptotic and Necrotic Cells[1] FREE

Sabine Jahr; Hannes Hentze; Sabine Englisch; Dieter Hardt; Frank O. Fackelmayer; Rolf-Dieter Hesch; Rolf Knippers

Check for updates

+ Author & Article Information

Cancer Res (2001) 61 (4): 1659–1665.

Article history

2001

2011

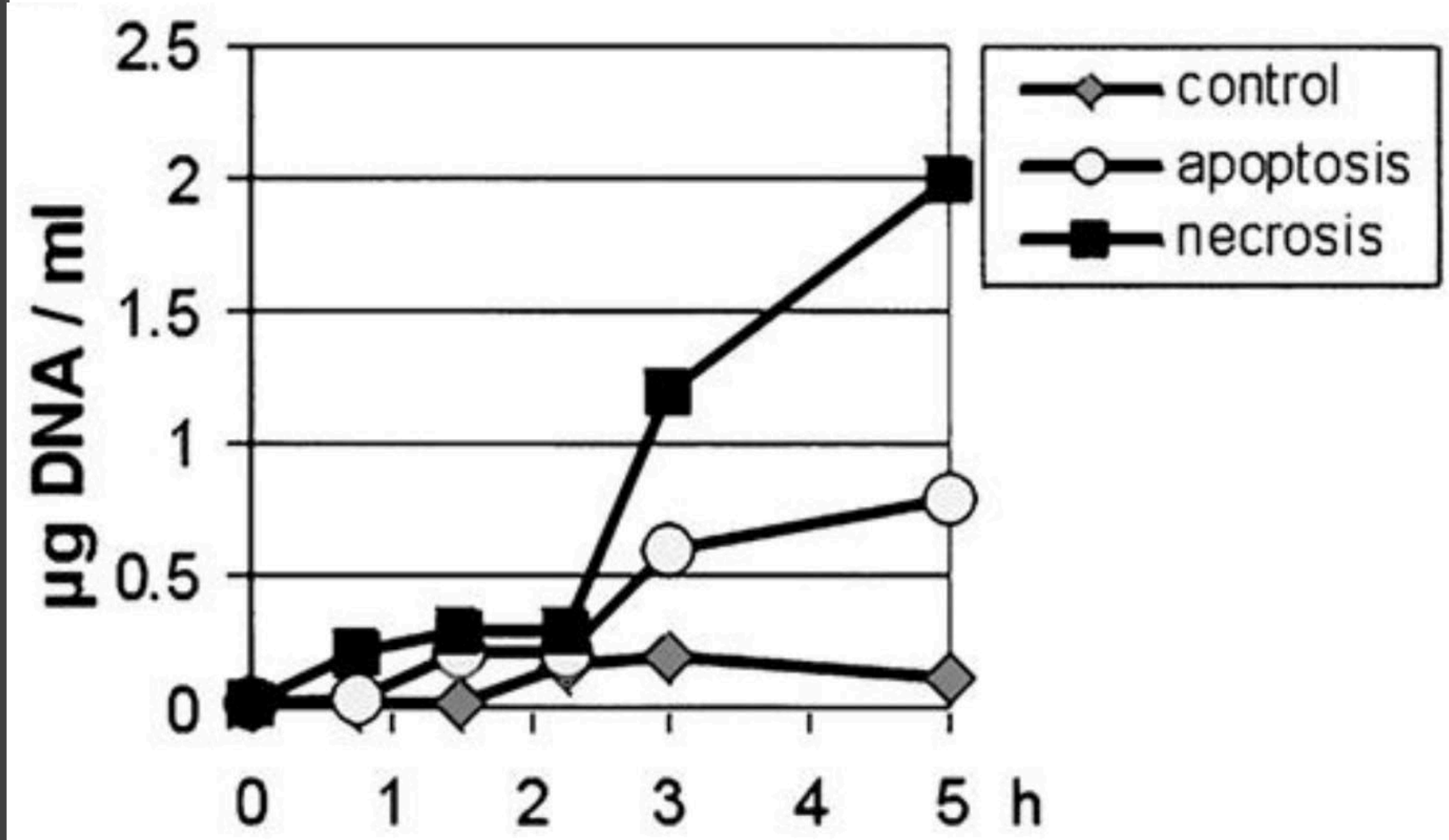
How is it released?

Necrosis?
Apoptosis?

In vitro and **in vivo** induced necrosis and apoptosis.

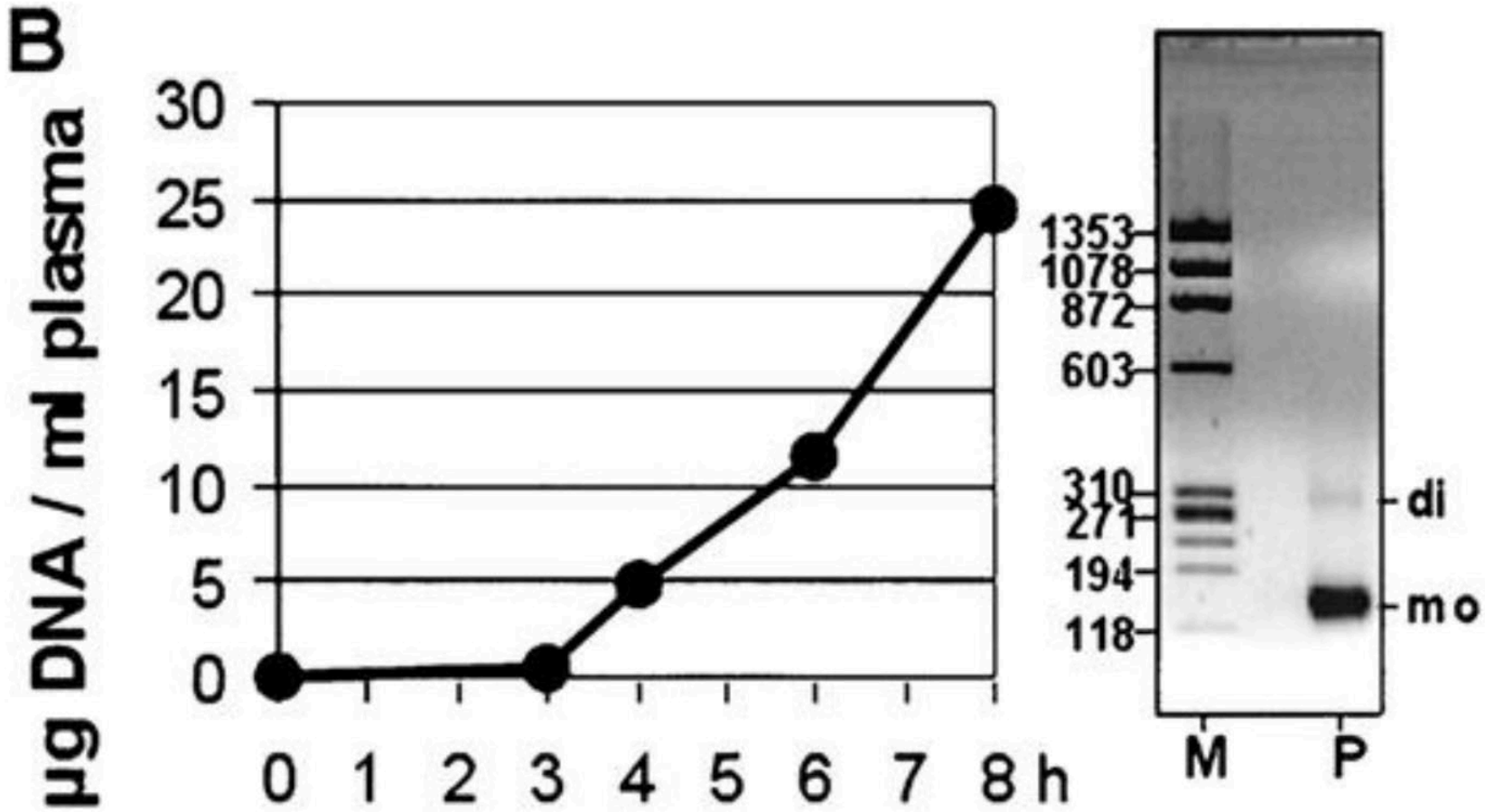
2001

IN VITRO



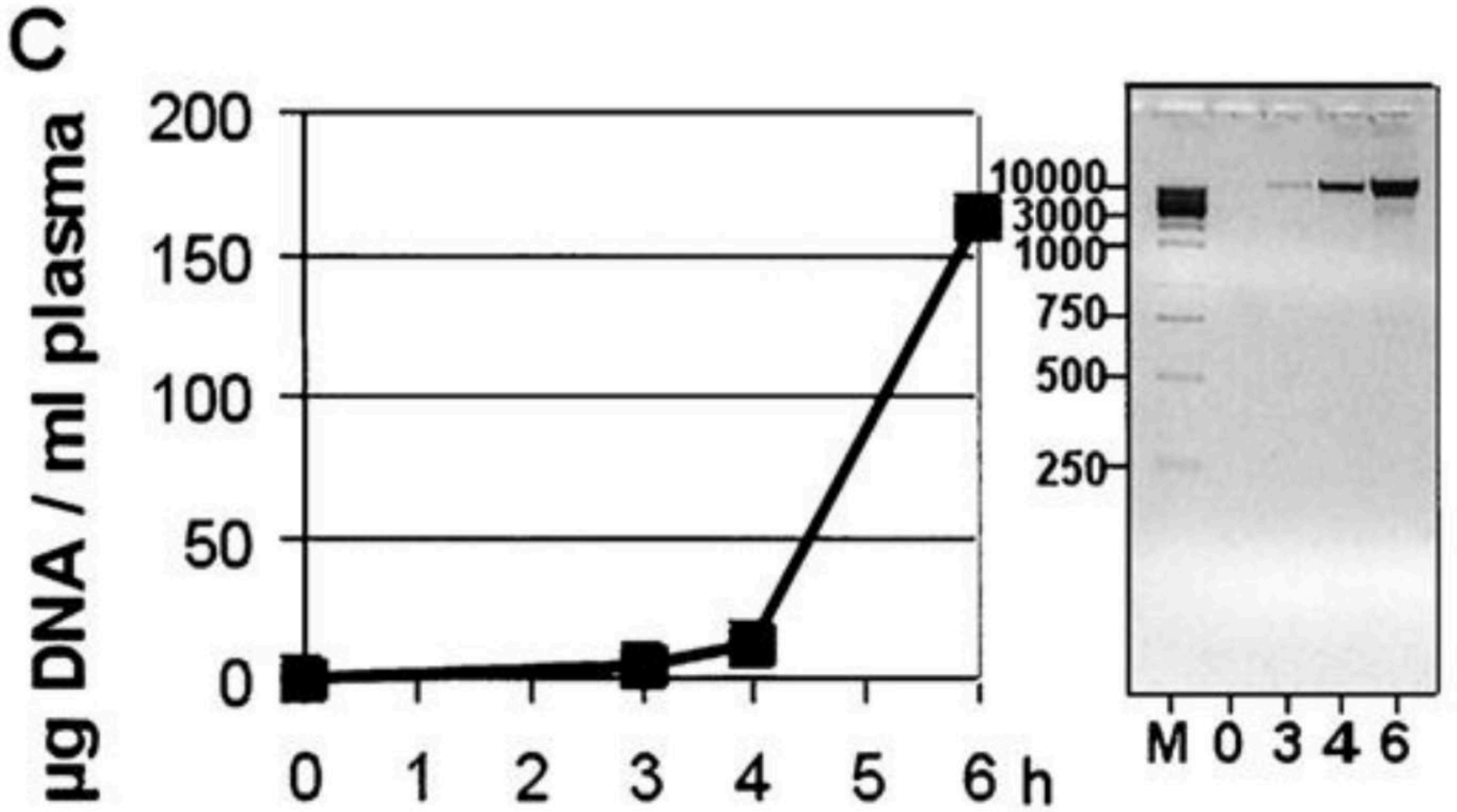
2001

IN VIVO APOPTOSIS



2001

IN VIVO NECROSIS



2001

Results

Necrosis ++
Apoptosis +

Neither T cells nor endothelial cells seem to contribute to plasma levels of DNA.

2019

CANCER BIOLOGY & THERAPY
2019, VOL. 20, NO. 8, 1057–1067
https://doi.org/10.1080/15384047.2019.1598759

Taylor & Francis
Taylor & Francis Group

REVIEW

Life and death of circulating cell-free DNA

Anatoli Kustanovich, Ruth Schwartz, Tamar Peretz, and Albert Grinshpun

Sharett Institute of Oncology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

ABSTRACT

Tumor-specific, circulating cell-free DNA in liquid biopsies is a promising source of biomarkers for minimally invasive serial monitoring of treatment responses in cancer management. We will review the current understanding of the origin of circulating cell-free DNA and different forms of DNA release (including various types of cell death and active secretion processes) and clearance routes. The dynamics of extracellular DNA in blood during therapy and the role of circulating DNA in pathophysiological processes (tumor-associated inflammation, NETosis, and pre-metastatic niche development) provide insights into the mechanisms that contribute to tumor development and metastases formation. Better knowledge of circulating tumor-specific cell-free DNA could facilitate the development of new therapeutic and diagnostic options for cancer management.

ARTICLE HISTORY
Received 28 November 2018
Revised 24 February 2019
Accepted 12 March 2019

KEYWORDS
Cell-free DNA; cancer; circulating tumor DNA; liquid biopsy; inflammation

2019

DNA release

CfDNA:
0 - 100 ng/ml in healthy subjects
0 - >1000 ng/ml in patients with cancer

tumor burden, but also ***might reflect tumor metabolism.***

necrosis and
oncosis (ischemic cell death)
pyroptosis
phagocytosis
active secretion
neutrophil extracellular trap release (NETosis),
excision repair

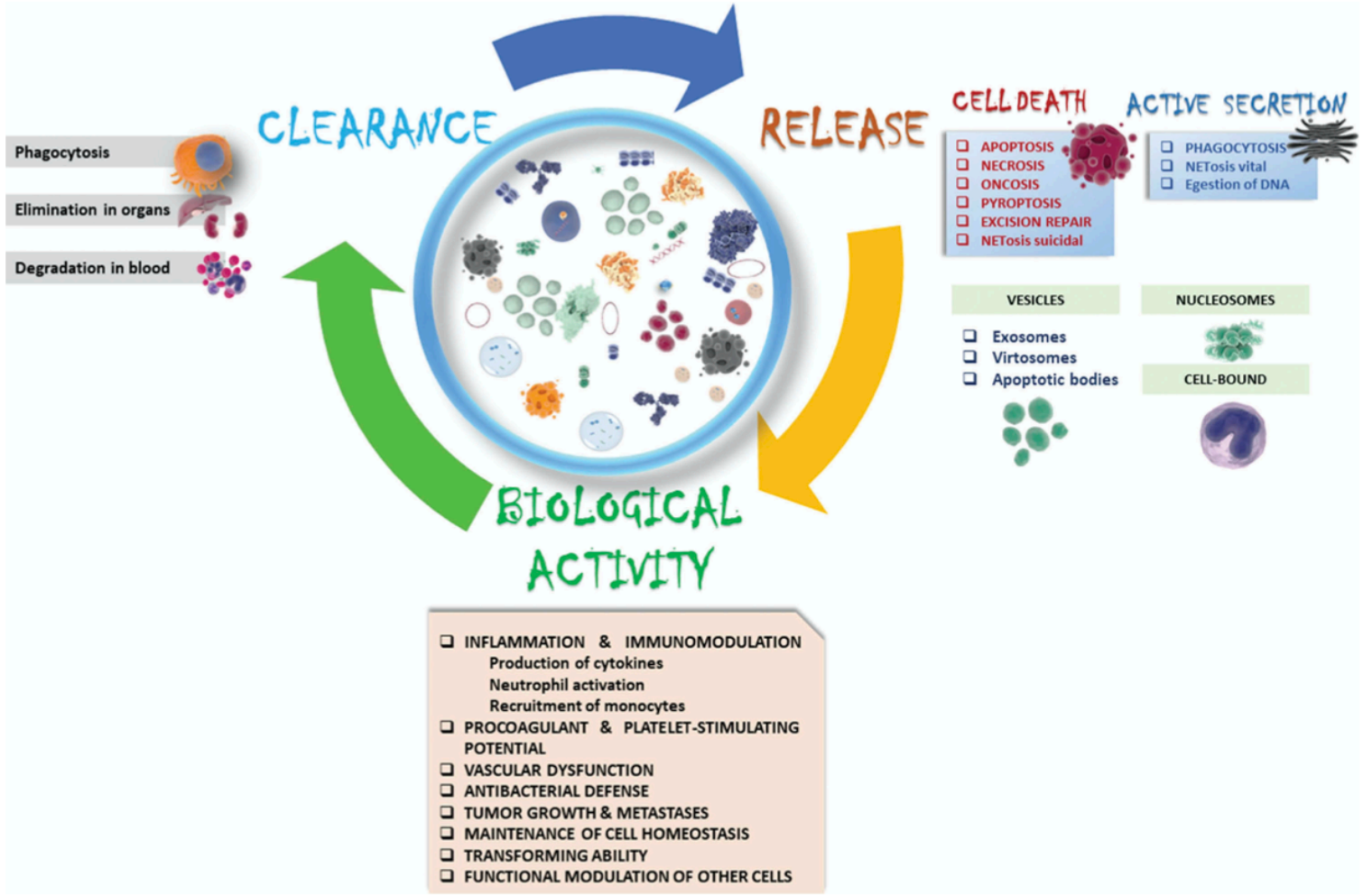


Figure 1. Cell-free circulating DNA life-cycle.

The three main components of cfDNA life are presented: release, biological activity, and clearance. The figure summarizes the well-described mechanisms of each component. Although in most clinical settings naked nuclear cfDNA is analyzed, it travels in various forms in body fluids: free, inside exosomes, bound to histones (nucleosomes), protected by transcriptional factors or are as part of immune-related components (such as NETs).cfDNA is not a passive biomarker of pathophysiological conditions, but plays an active role in multiple processes such as inflammation, immunomodulation, tumor growth promotion, etc..

Approches actuelles

2020

CONSENSUS STATEMENT

OPEN

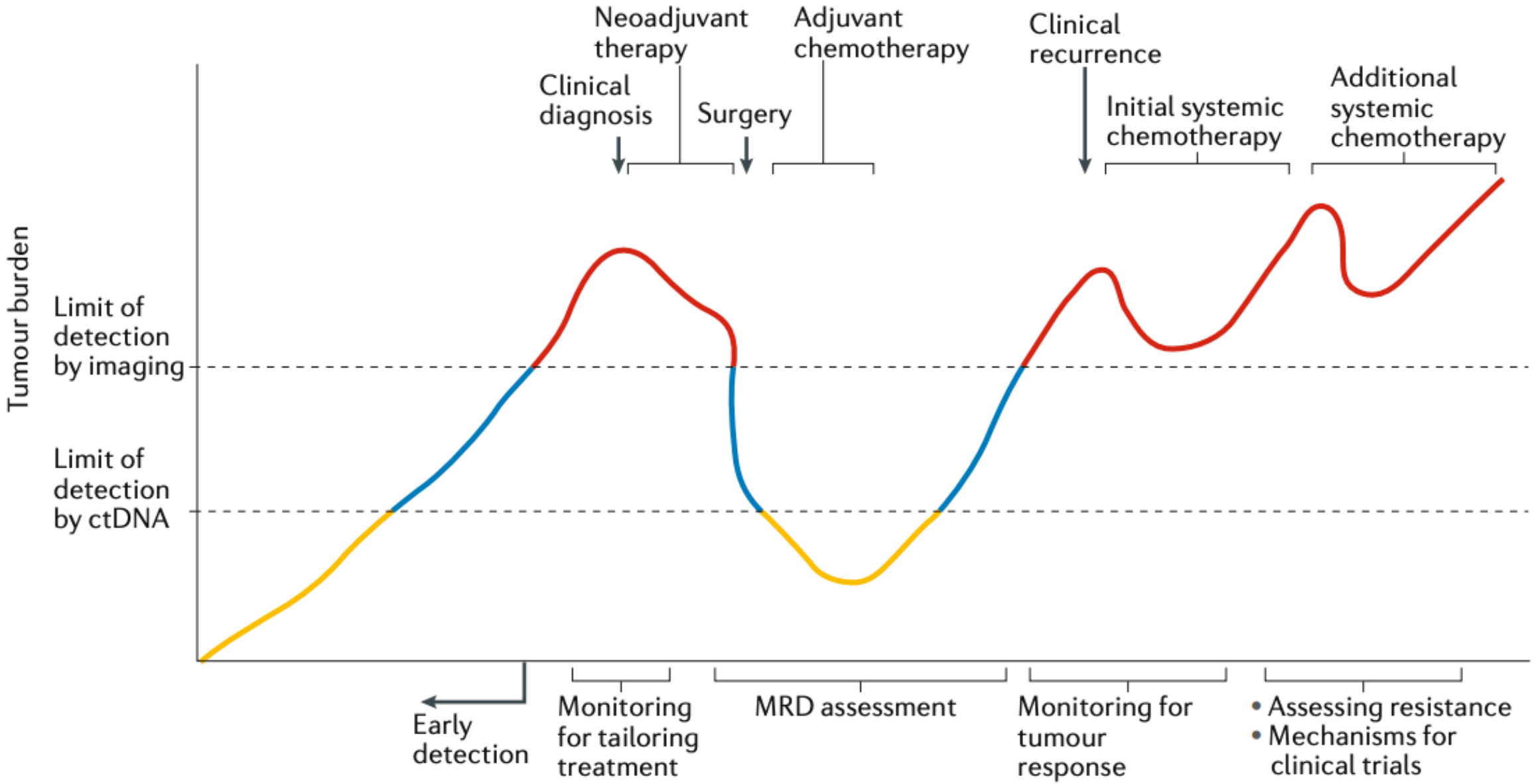
ctDNA applications and integration in colorectal cancer: an NCI Colon and Rectal–Anal Task Forces whitepaper

Arvind Dasari[1,40]✉, Van K. Morris[1,40], Carmen J. Allegra[2], Chloe Atreya[3], Al B. Benson III[4], Patrick Boland[5], Ki Chung[6], Mehmet S. Copur[7], Ryan B. Corcoran[8], Dustin A. Deming[9], Andrea Dwyer[10], Maximilian Diehn[11], Cathy Eng[1], Thomas J. George[12], Marc J. Gollub[13], Rachel A. Goodwin[14], Stanley R. Hamilton[15], Jaclyn F. Hechtman[16], Howard Hochster[17], Theodore S. Hong[18], Federico Innocenti[19], Atif Iqbal[20], Samuel A. Jacobs[21], Hagen F. Kennecke[22], James J. Lee[23], Christopher H. Lieu[24], Heinz-Josef Lenz[25], O. Wolf Lindwasser[26], Clara Montagut[27], Bruno Odisio[28], Fang-Shu Ou[29], Laura Porter[30], Kanwal Raghav[1], Deborah Schrag[31], Aaron J. Scott[32], Qian Shi[29], John H. Strickler[33], Alan Venook[34], Rona Yaeger[35], Greg Yothers[36], Y. Nancy You[37], Jason A. Zell[38,39] and Scott Kopetz[1]

Detection:
50% in those with non-metastatic disease
90% in patients with metastatic disease

ctDNA has the **potential to change clinical** practice

-detection of minimal residual disease, **(MRD)**
-management of patients with rectal cancer,
-monitoring responses to therapy,
-and tracking clonal dynamics in response to targeted therapies and other systemic treatments.



Approche 1
PCR

Droplet Digital PCR
or
BEAMING (beads, emulsion, amplification, magnetics)

La première approche **cible** une **altération** génétique **connue** et correspondant le plus souvent à des mutations d'intérêt ou identifiées préalablement dans le tissu tumoral.

Ultrasensible mais dépend de la mutation.

Approche 2
NGS

En l’absence d’altérations connues ou en cas de nécessité d’analyser un grand nombre d’altérations, c’est une méthode de séquençage à haut débit ou Next-Generation Sequencing (NGS): panels de gènes ou hotspots.

Approche 3

Multidimentionnelle

Méthylation

Modification

histones

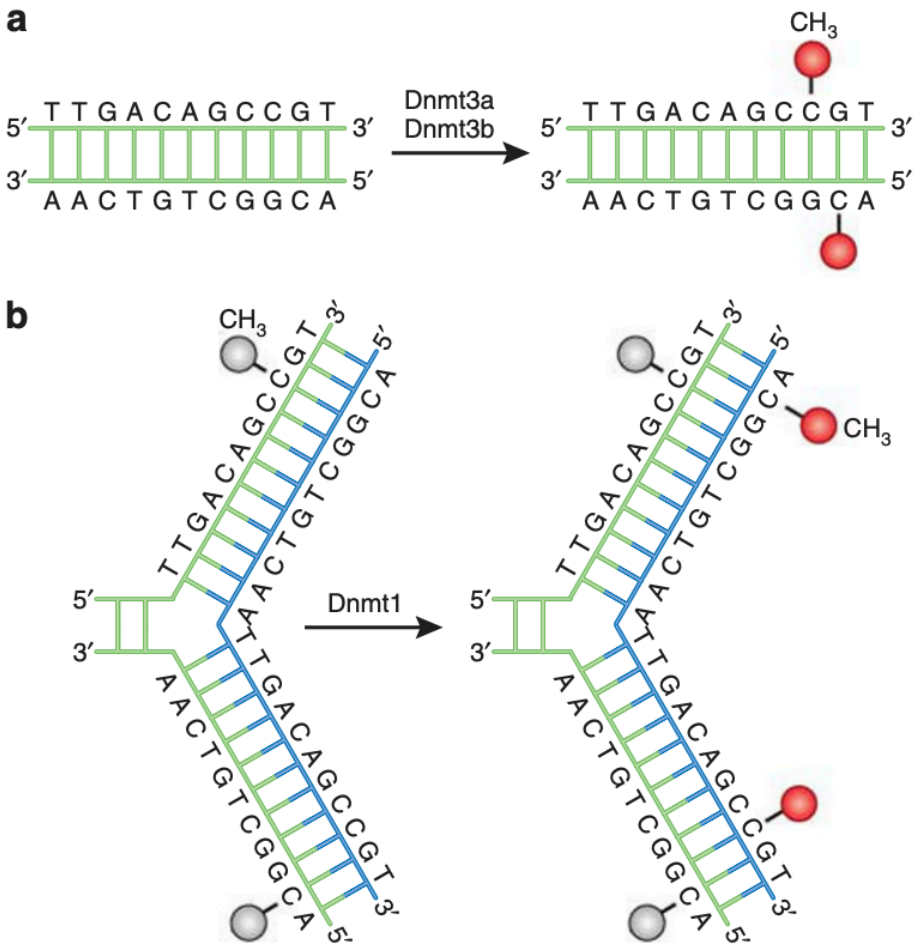
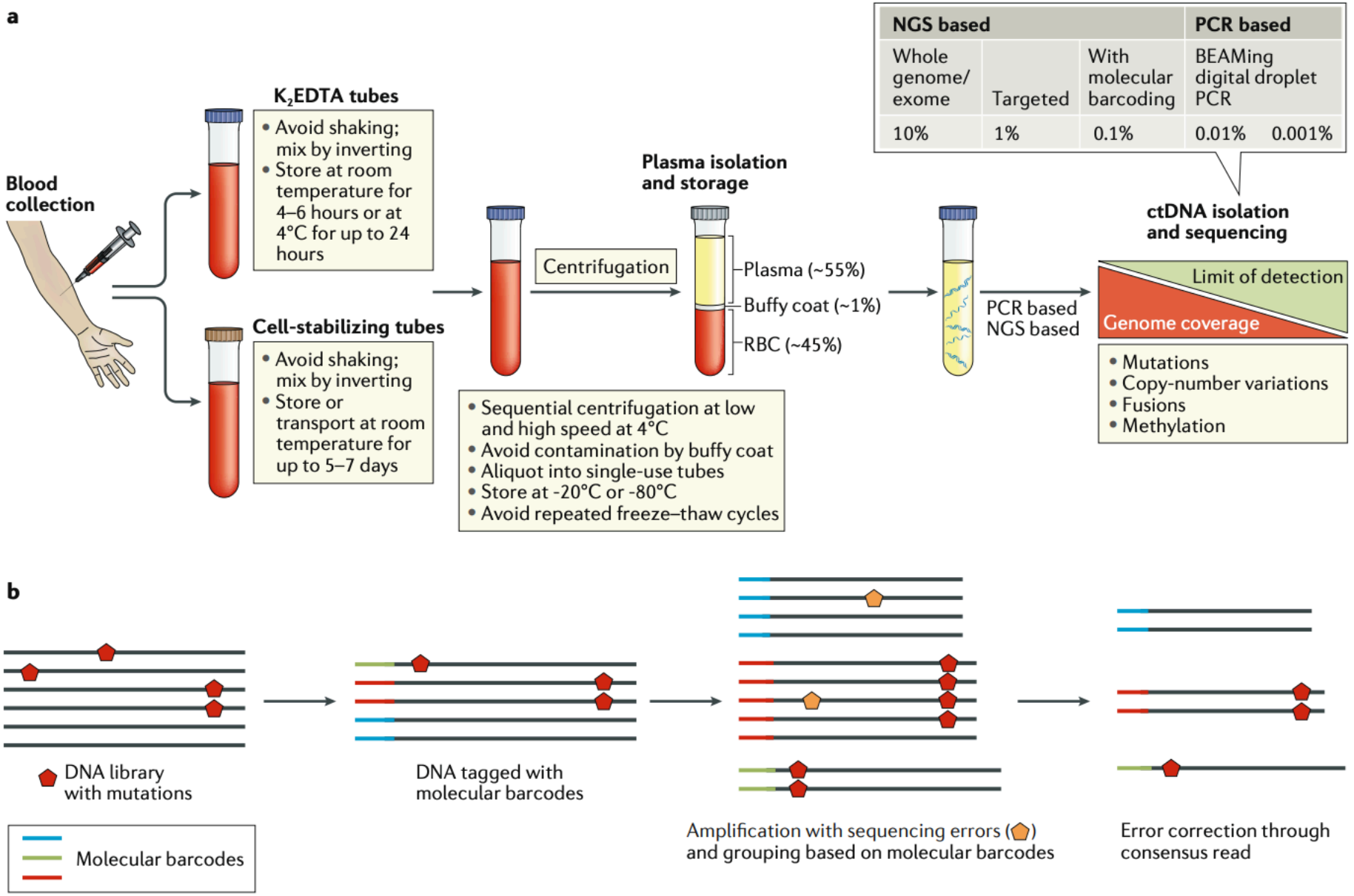
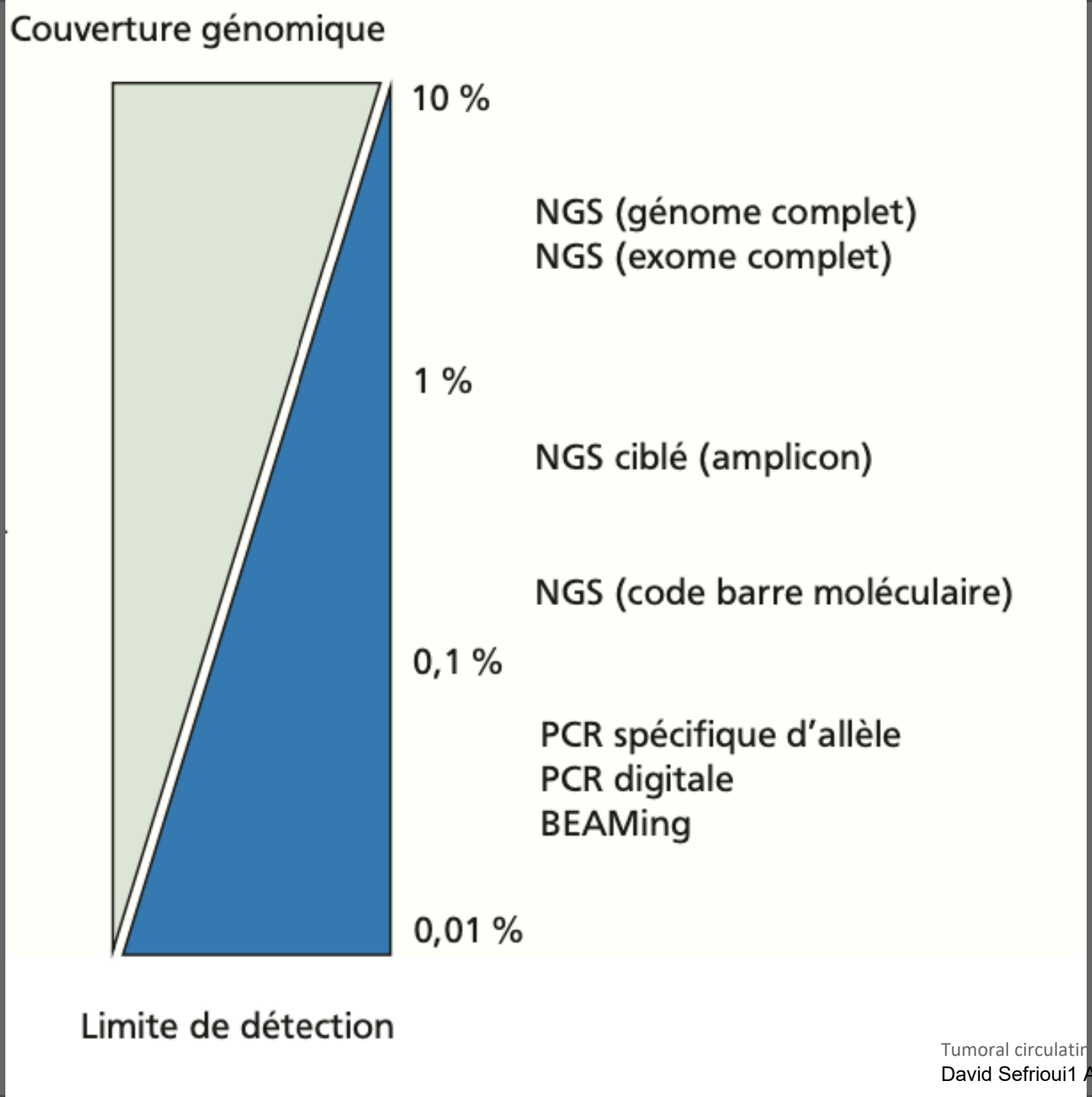


Figure 1. DNA methylation pathways. A family of DNA methyltransferases (Dnmts) catalyzes the transfer of a methyl group from *S*-adenyl methionine (SAM) to the fifth carbon of cytosine residue to form 5-methylcytosine (5mC). (a) Dnmt3a and Dnmt3b are the *de novo* Dnmts and transfer methyl groups (red) onto naked DNA. (b) Dnmt1 is the maintenance Dnmt and maintains DNA methylation pattern during replication. When DNA undergoes semiconservative replication, the parental DNA stand retains the original DNA methylation pattern (gray). Dnmt1 associates at the replication foci and precisely replicates the original DNA methylation pattern by adding methyl groups (red) onto the newly formed daughter strand (blue).

Moore, L., Le, T. & Fan, G. DNA Methylation and Its Basic Function. *Neuropsychopharmacol* **38**, 23–38 (2013). https://doi.org/10.1038/npp.2012.112


a
Blood collection
K2EDTA tubes
• Avoid shaking; mix by inverting
• Store at room temperature for 4–6 hours or at 4°C for up to 24 hours
Cell-stabilizing tubes
• Avoid shaking; mix by inverting
• Store or transport at room temperature for up to 5–7 days
Centrifugation
Plasma isolation and storage
Plasma (~55%)
Buffy coat (~1%)
RBC (~45%)
• Sequential centrifugation at low and high speed at 4°C
• Avoid contamination by buffy coat
• Aliquot into single-use tubes
• Store at -20°C or -80°C
• Avoid repeated freeze–thaw cycles
PCR based
NGS based
ctDNA isolation and sequencing
NGS based
Whole genome/ exome
Targeted
With molecular barcoding
PCR based
BEAMing digital droplet PCR
10%
1%
0.1%
0.01%
0.001%
Limit of detection
Genome coverage
• Mutations
• Copy-number variations
• Fusions
• Methylation
b
DNA library with mutations
DNA tagged with molecular barcodes
Amplification with sequencing errors (⬟) and grouping based on molecular barcodes
Error correction through consensus read
Molecular barcodes


Couverture génomique
10 %
NGS (génome complet)
NGS (exome complet)
1 %
NGS ciblé (amplicon)
NGS (code barre moléculaire)
0,1 %
PCR spécifique d'allèle
PCR digitale
BEAMing
0,01 %
Limite de détection

Un exemple-clé: le stade II opéré

Chimiothérapie adjuvante?

European Journal of Cancer 159 (2021) 24–33

Available online at www.sciencedirect.com

ScienceDirect

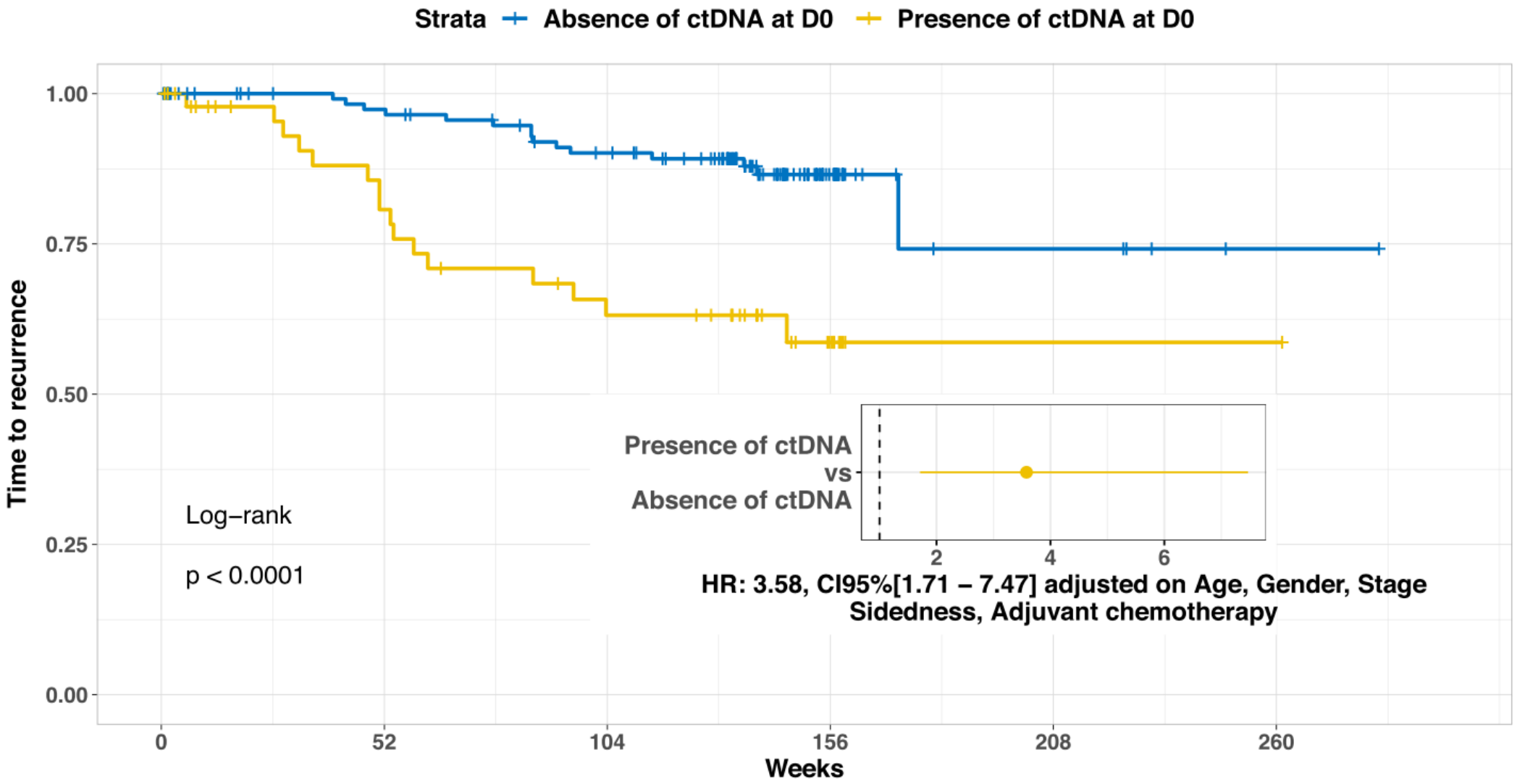
journal homepage: www.ejcancer.com

Original Research

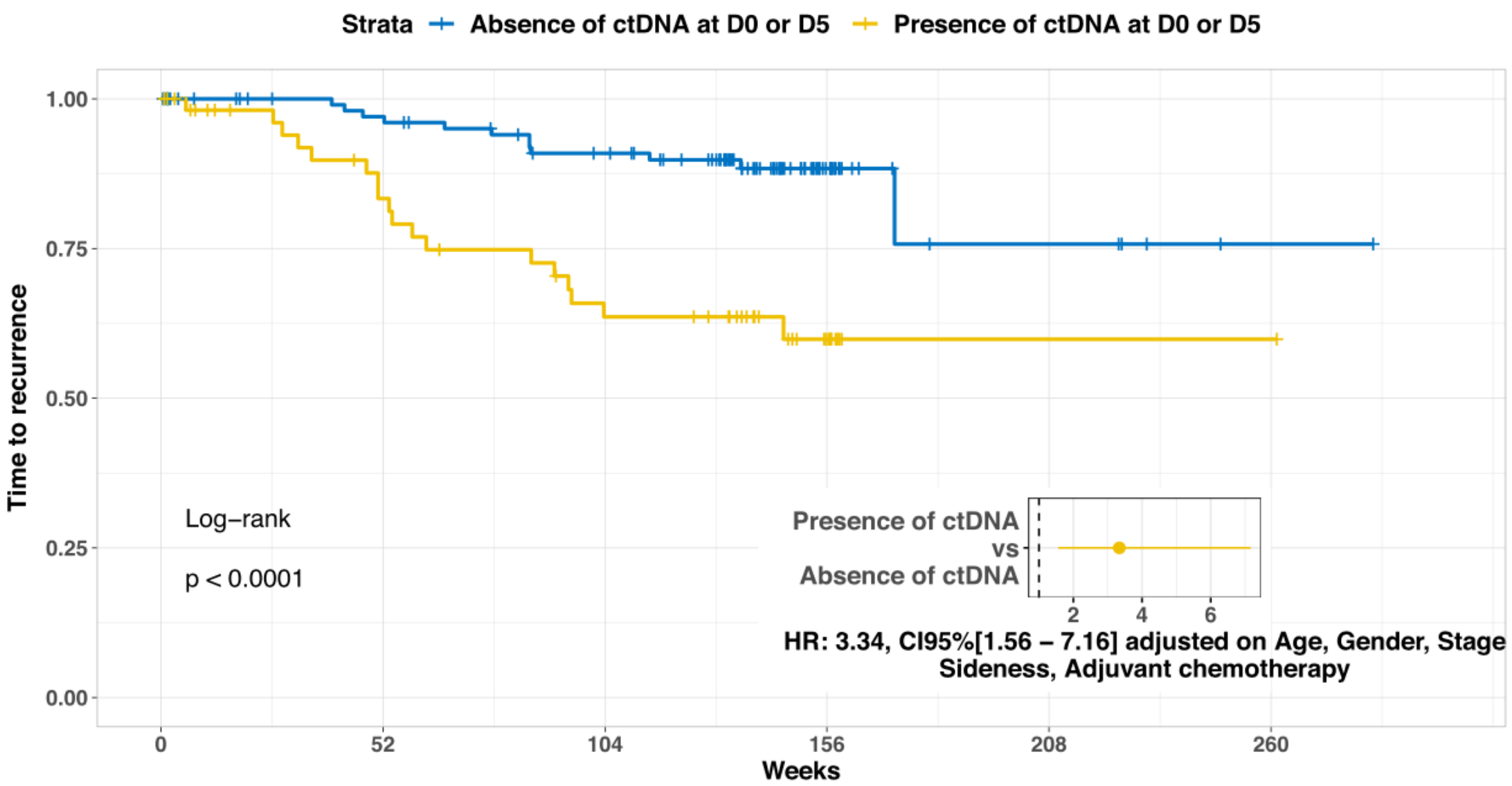
Circulating tumor DNA is a prognostic marker of tumor recurrence in stage II and III colorectal cancer: multicentric, prospective cohort study (ALGECOLS)

Leonor Benhaim [a,b,1], Olivier Bouché [c,1], Corinne Normand [a,1], Audrey Didelot [a], Claire Mulot [a,d], Delphine Le Corre [a], Sonia Garrigou [a], Juliette Djadi-Prat [e], Shu-Fang Wang-Renault [a], Karla Perez-Toralla [a], Deniz Pekin [a], Geoffroy Poulet [a,f], Bruno Landi [g], Julien Taieb [a,g], Marie Selvy [h], Jean-Francois Emile [i], Thierry Lecomte [j], Helene Blons [a,k], Gilles Chatellier [e], Darren R. Link [l], Valerie Taly [a,**,1], Pierre Laurent-Puig [a,k,*,1]

Avant chirurgie, marqueur pronostique...



...après chirurgie, MRD



biomarker-driven adjuvant therapy

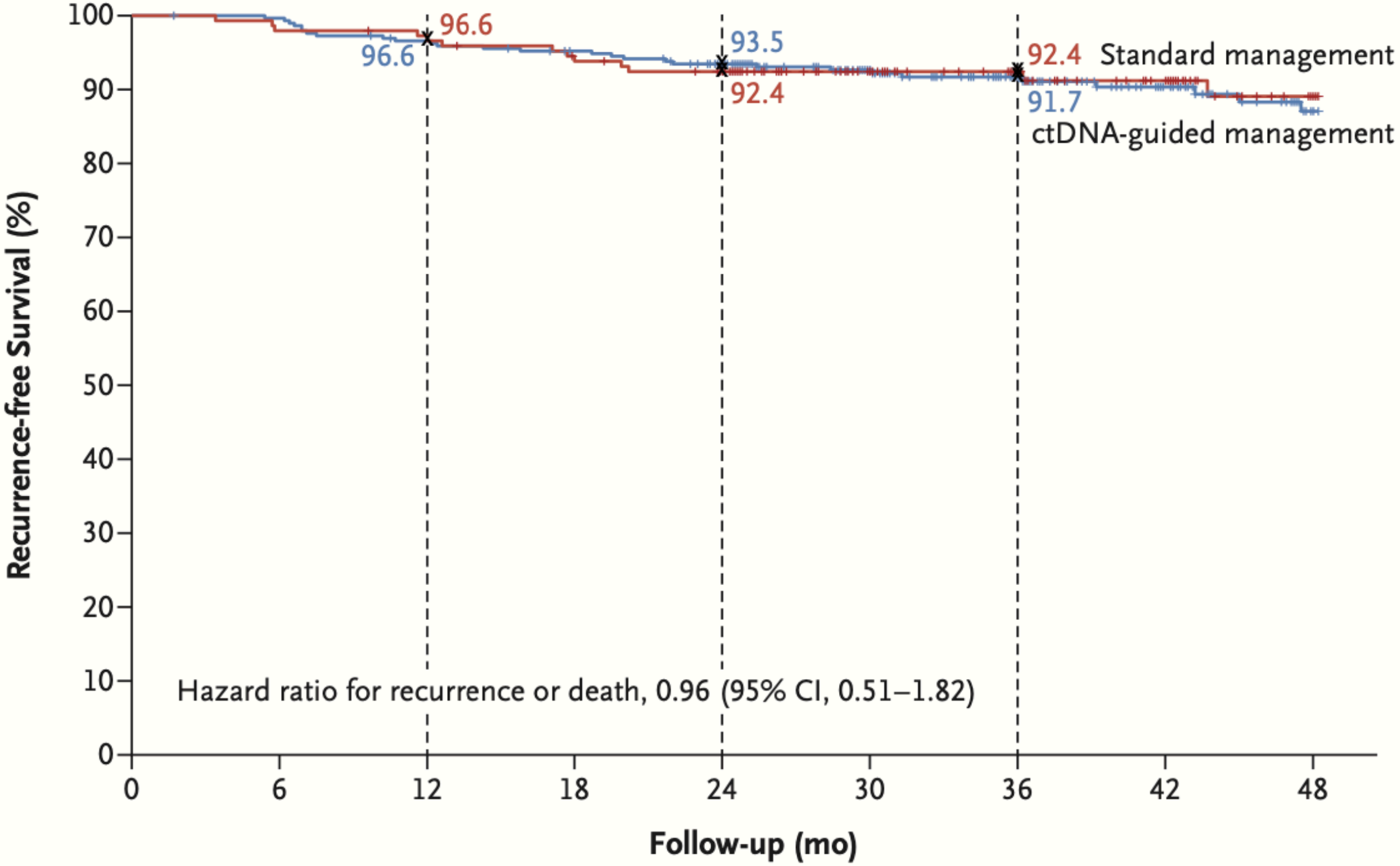
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 16, 2022 VOL. 386 NO. 24

Circulating Tumor DNA Analysis Guiding Adjuvant Therapy in Stage II Colon Cancer

Table 1. Characteristics of the Patients at Baseline in the Intention-to-Treat Population.*

Characteristic	Standard Management (N=147)	ctDNA-Guided Management (N=294)	Overall (N=441)
Male sex — no. (%)	81 (55)	154 (52)	235 (53)
Median age (range) — yr	62 (28–84)	65 (30–94)	64 (28–94)
Age group — no. (%)			
≤70 yr	113 (77)	207 (70)	320 (73)
>70 yr	34 (23)	87 (30)	121 (27)
ECOG performance-status score — no./total no. (%)†			
0	124/147 (84)	226/293 (77)	350/440 (80)
1	20/147 (14)	65/293 (22)	85/440 (19)
2	3/147 (2)	2/293 (1)	5/440 (1)
Type of center — no. (%)			
Metropolitan	121 (82)	240 (82)	361 (82)
Regional	26 (18)	54 (18)	80 (18)
Primary tumor site — no. (%)‡			
Left side	78 (53)	126 (43)	204 (46)
Right side	69 (47)	168 (57)	237 (54)
Tumor stage — no. (%)			
T3	127 (86)	250 (85)	377 (85)
T4	20 (14)	44 (15)	64 (15)
Poor tumor differentiation — no. (%)	17 (12)	43 (15)	60 (14)
Lymph node yield <12 — no. (%)	7 (5)	13 (4)	20 (5)
Tumor perforation — no. (%)	7 (5)	7 (2)	14 (3)
Bowel obstruction — no./total no. (%)†	18/147 (12)	26/291 (9)	44/438 (10)
Lymphovascular invasion — no. (%)	38 (26)	82 (28)	120 (27)
Deficient mismatch repair — no. (%)	27 (18)	59 (20)	86 (20)
Clinical risk group — no./total no. (%)§			
High	60/147 (41)	116/293 (40)	176/440 (40)
Low	87/147 (59)	177/293 (60)	264/440 (60)
Median time from surgery to randomization (IQR) — days	33 (28–41)	32 (28–39)	32 (28–39.5)


Recurrence-free Survival (%)
100
90
80
70
60
50
40
30
20
10
0
96.6
96.6
93.5
92.4
92.4
91.7
Standard management
ctDNA-guided management
Hazard ratio for recurrence or death, 0.96 (95% CI, 0.51–1.82)
0
6
12
18
24
30
36
42
48
Follow-up (mo)

RESULTS

Of the 455 patients who underwent randomization, 302 were assigned to ctDNA-guided management and 153 to standard management. The median follow-up was 37 months. A lower percentage of patients in the ctDNA-guided group than in the standard-management group received adjuvant chemotherapy (15% vs. 28%; relative risk, 1.82; 95% confidence interval [CI], 1.25 to 2.65). In the evaluation of 2-year recurrence-free survival, ctDNA-guided management was noninferior to standard management (93.5% and 92.4%, respectively; absolute difference, 1.1 percentage points; 95% CI, −4.1 to 6.2 [noninferiority margin, −8.5 percentage points]). Three-year recurrence-free survival was 86.4% among ctDNA-positive patients who received adjuvant chemotherapy and 92.5% among ctDNA-negative patients who did not.

Et dans la chirurgie hépatique?

RESEARCH ARTICLE

Circulating tumor DNA dynamics and recurrence risk in patients undergoing curative intent resection of colorectal cancer liver metastases: A prospective cohort study

Jeanne Tie[1,2,3,4]*, Yuxuan Wang[5], Joshua Cohen[5], Lu Li[5], Wei Hong[1], Michael Christie[1,4,6], Hui Li Wong[1,3], Suzanne Kosmider[2], Rachel Wong[1,7,8], Benjamin Thomson[3,4,6], Julian Choi[2], Adrian Fox[7], Kathryn Field[3], Matthew Burge[9], Jenny Shannon[10], Dusan Kotasek[11], Niall C. Tebbutt[12], Christos Karapetis[13], Craig Underhill[14], Andrew Haydon[15], Joy Schaeffer[5], Janine Ptak[5], Cristian Tomasetti[5,16], Nicholas Papadopoulos[5], Kenneth W. Kinzler[5], Bert Vogelstein[5‡], Peter Gibbs[1,2,4‡]

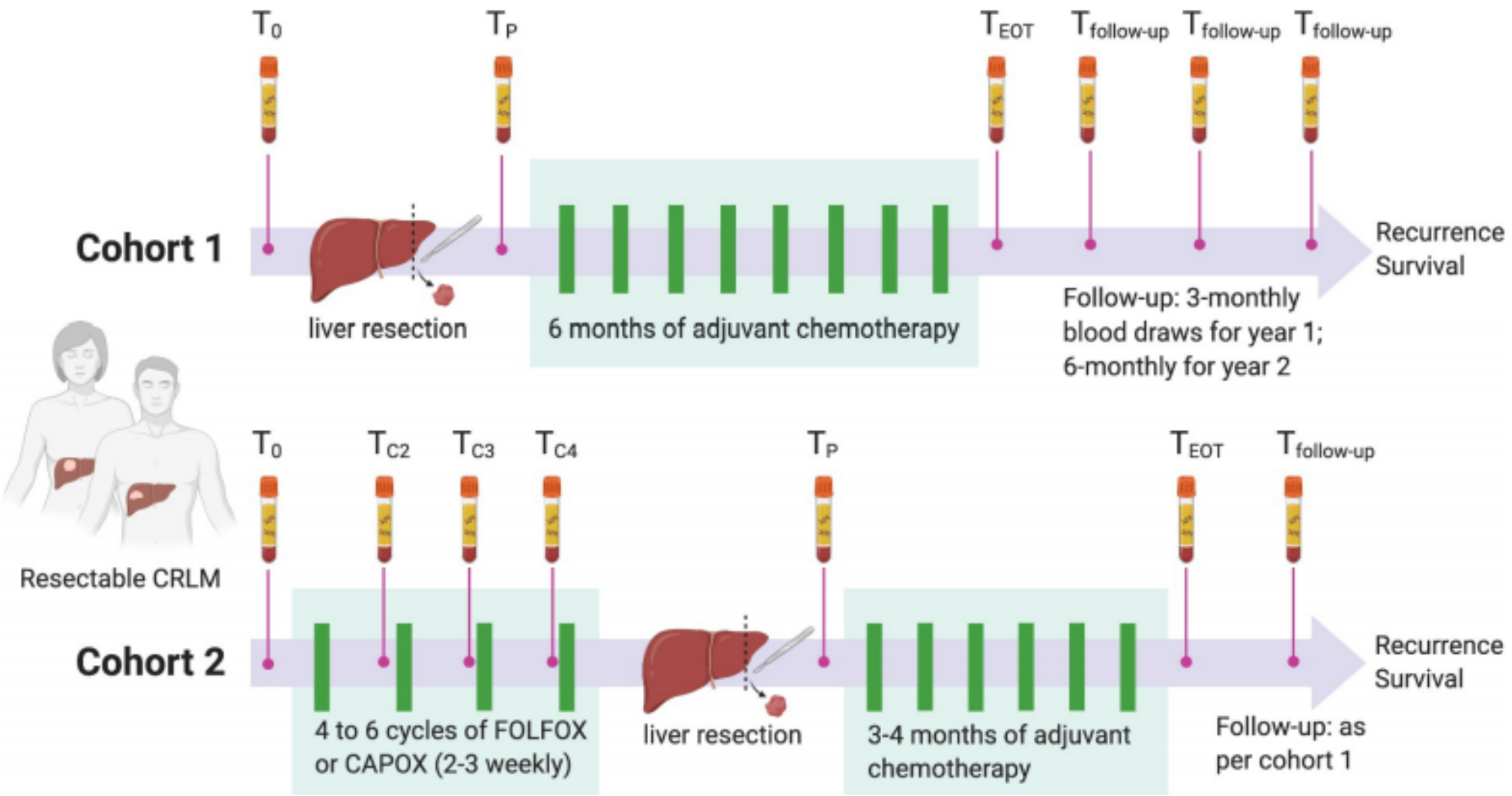


Fig 1. Study design. Study schema showing blood collection time points in Cohort 1 (upfront liver resection) and Cohort 2 (neoadjuvant chemotherapy). The primary objective of the study was to assess the prognostic impact of postoperative ctDNA (T_P) on recurrence-free survival in the total population. T_0 = baseline, T_{C2} = pre-cycle 2, T_{C3} = pre-cycle 3, T_{C4} = pre-cycle 4, T_P = 4 to 10 weeks postoperative, T_{EOT} = end of treatment, $T_{follow\text{-}up}$ = follow-up. CRLM, colorectal cancer liver metastasis; ctDNA, circulating tumor DNA.

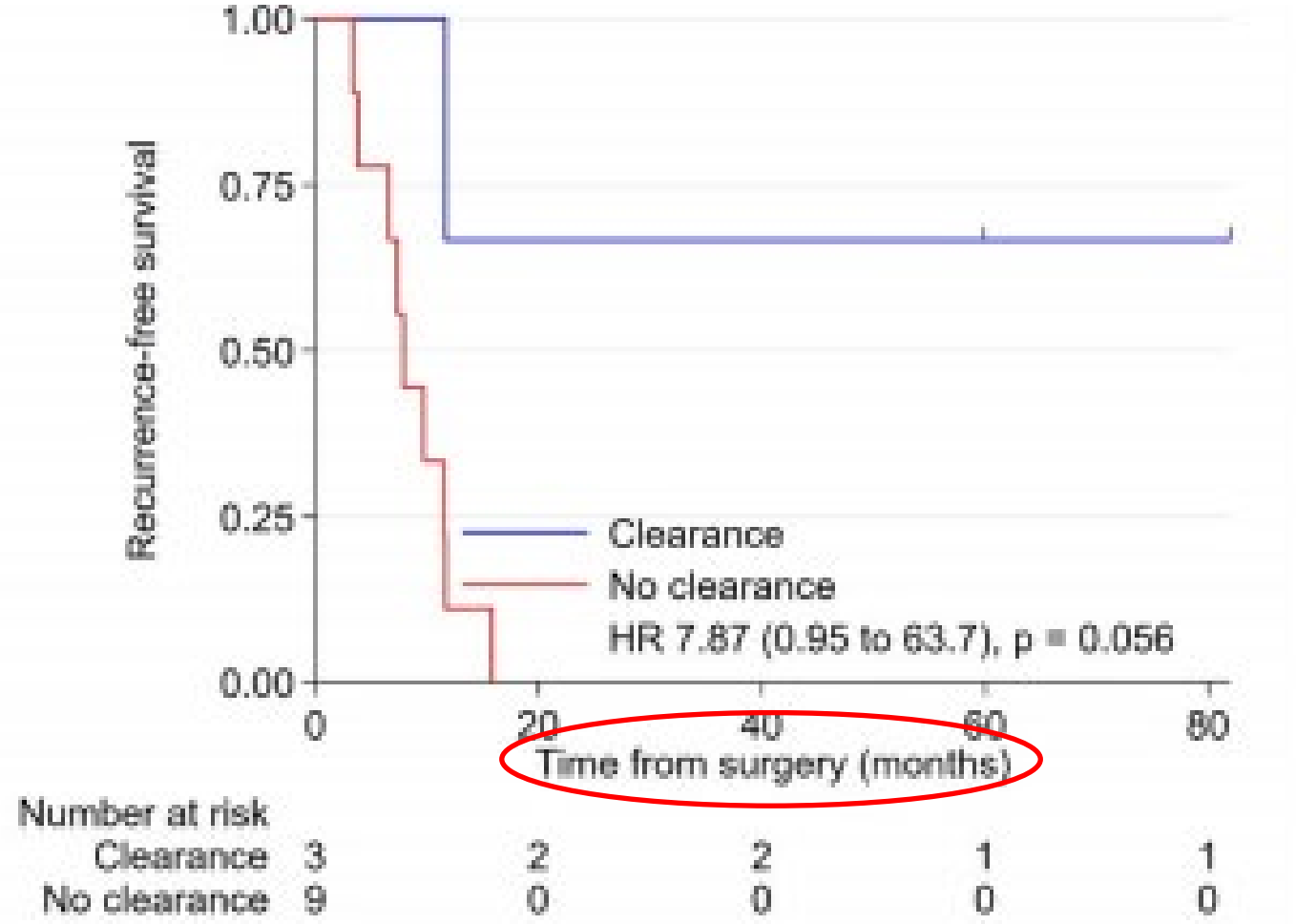
https://doi.org/10.1371/journal.pmed.1003620.g001

ctDNA was detected in 24% of patients immediately after surgery

ctDNA+: recurrence risk of **83% compared to only 31%** in those with undetectable ctDNA after surgery.

All (100%) patients with detectable postoperative ctDNA who **failed to clear their ctDNA** following adjuvant chemotherapy experienced **recurrence** (median time to recurrence of **2.2 months** after completion of chemotherapy)

67% of patients whose ctDNA became undetectable after chemotherapy remained disease-free.


1.00
0.75
0.50
0.25
0.00
Recurrence-free survival
Clearance
No clearance
HR 7.87 (0.95 to 63.7), p = 0.056
0
20
40
60
80
Time from surgery (months)
Number at risk
Clearance 3 2 2 1 1
No clearance 9 0 0 0 0

cells

MDPI

Article

Circulating Tumor Cells and Circulating Tumor DNA Detection in Potentially Resectable Metastatic Colorectal Cancer: A Prospective Ancillary Study to the Unicancer Prodige-14 Trial

François-Clément Bidard [1,2,3], Nicolas Kiavue [1,*], Marc Ychou [4,5], Luc Cabel [1,2,3], Marc-Henri Stern [6], Jordan Madic [2], Adrien Saliou [2], Aurore Rampanou [2], Charles Decraene [2,7], Olivier Bouché [8], Michel Rivoire [9], François Ghiringhelli [10], Eric Francois [11], Rosine Guimbaud [12], Laurent Mineur [13], Faiza Khemissa-Akouz [14], Thibault Mazard [4], Driffa Moussata [15], Charlotte Proudhon [2], Jean-Yves Pierga [1,2,16], Trevor Stanbury [17], Simon Thézenas [18] and Pascale Mariani [19]

CRC patients with initially defined unresectable **liver-only metastases**

2-CTx (FOLFOX or FOLFIRI)
Vs
3-CTx (FOLFIRINOX)

(plus bevacizumab/cetuximab by RAS status)

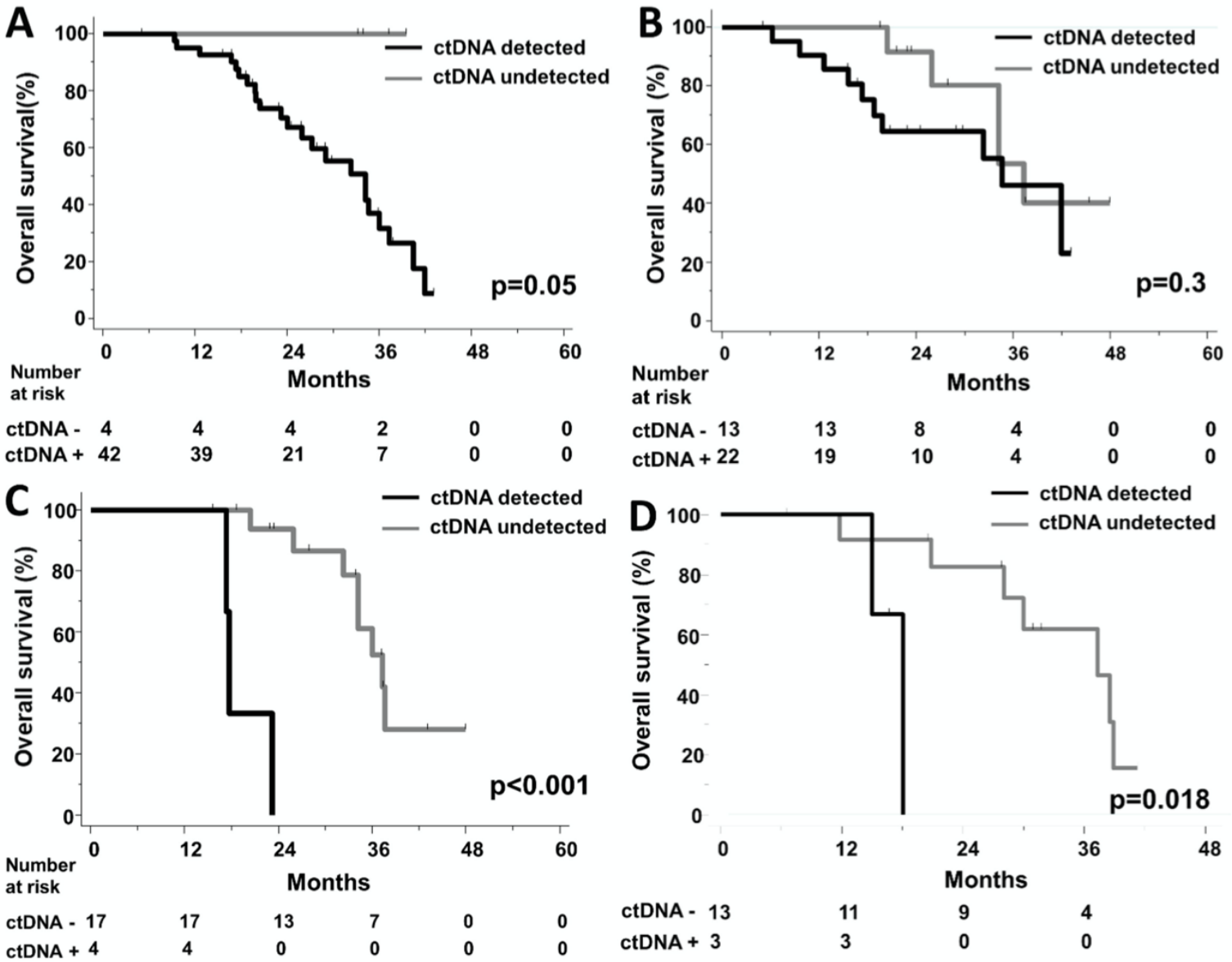


Figure 5. Kaplan–Meier curves for Overall Survival according to ctDNA detection (**A**) at baseline, (**B**) at 4 weeks, (**C**) before liver surgery (**D**) Kaplan–Meier curve for post-operative Overall Survival according to ctDNA detection before liver surgery.

« More interestingly, the absence of ctDNA at 4 weeks was correlated with a very high R0/R1 resection rate of LM (85%), suggesting that this **biomarker could help decide whether liver surgery is appropriate for patients »**

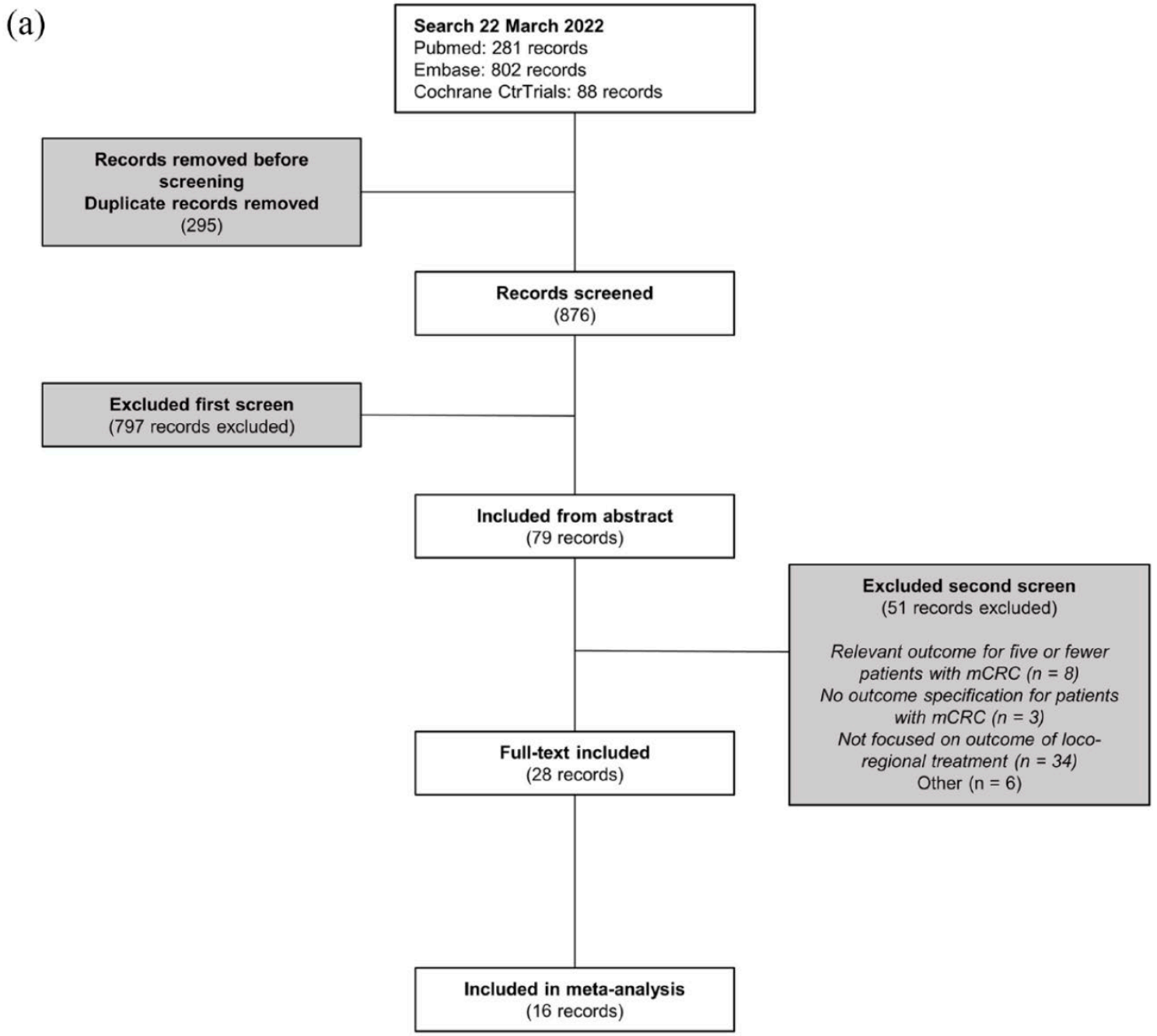
Finally, in patients referred to surgery for LM resection, persistently detectable **ctDNA levels before surgery** was associated with short post-surgical OS, suggesting that **LM were not fully responding to therapy and/or that extra-hepatic micro-metastases were present. »**

Et dans l’ablation?

THERAPEUTIC ADVANCES in
Medical Oncology

Circulating DNA in patients undergoing loco-regional treatment of colorectal cancer metastases: a systematic review and meta-analysis

Louise B. Callesen, Tana Takacova, Julian Hamfjord, Florian Würschmidt, Karl J. Oldhafer, Roland Brüning, Dirk Arnold and Karen-Lise G. Spindler



LIVER

Resection (*n*=14/28)
DEBIRI-TACE (*n*=1/28),
HAI (*n*=1/28)
Combined RFA/ (SIRT)
(*n*=1/28).

OTHER SITES

Resection (*n*=6/28)
Ablative radiotherapy
(*n*=1/28)
Varions treatment modalities
(*n* = 1/28)
(CRS-HIPEC) ((*n*=1/28)

In vivo effects of thermal ablation
coagulation necrosis
apoptosis
direct and **indirect** and indirect mechanisms including the activation of antitumor immune response

ctDNA dynamics ???

Expérience locale

Inclusion criteria

1. Histologically confirmed colorectal cancer.
2. **Metastatic disease referred to thermo-ablation with intent-to-cure**
3. No antiangiogenic therapy 2 weeks prior to thermo-ablation.
4. At least one target lesion (RECIST1.1), measurable with CT or MRI:
5. Age ≥ 18.
6. Performance status ≤ 2.
7. Women of childbearing potential must have a negative serum pregnancy test prior to registration.
8. Patients with a social security in compliance with the French law
9. Patients must be willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures.
10. Voluntarily signed and dated written informed consents prior to any study specific procedure.

Exclusion criteria

1. Inadequate kidney, liver functions.
2. Haematological contra indications to percutaneous approaches.
3. Contra-indications to general anesthesia.
4. Active, uncontrolled bacterial, viral, or fungal infections.
5. Females who are pregnant or breast-feeding.

NGS was performed with a dedicated panel of 92 amplicons (Ion AmpliSeq Colon-Lung Cancer Research Panel version 2; Life Technologies, Carlsbad, CA, USA)

covering > 500 hotspot mutations in KRAS, EGFR, BRAF, PIK3CA, AKT1, ERBB2, PTEN, NRAS, STK11, MAP2K1, ALK, DDR2, CTNNB1, MET, TP53, SMAD4, FBXW7, FGFR3, NOTCH1, ERBB4, FGFR1, and FGFR2.

INCLUSION: CRCLM

THERMAL ABLATION

H0 H2 H24 D15 D30 D60 D90

Ct DNA

RI

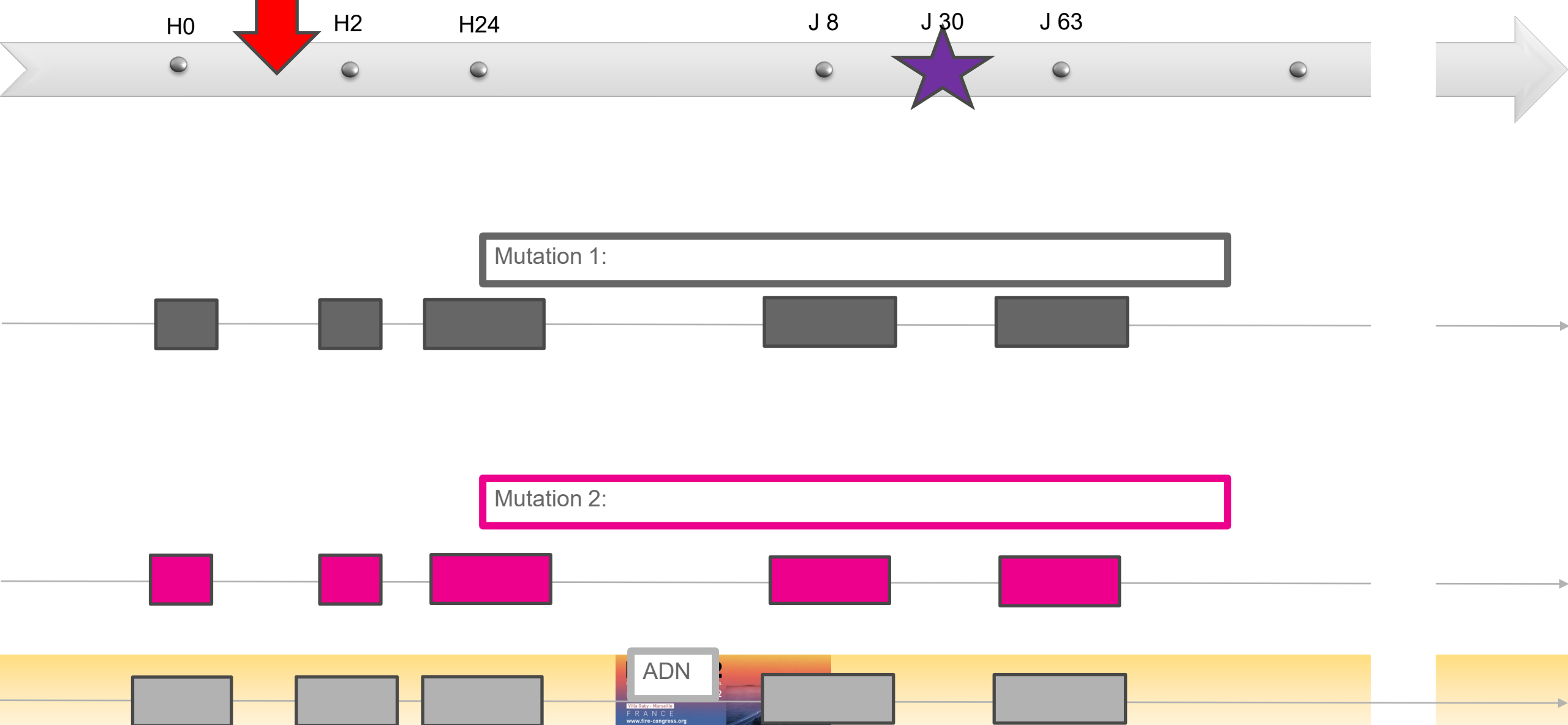
MACHINE LEARNING

CRCLM: colorectal cancer liver metastases
Ct DNA: circulating tumor DNA
RI: radiological imaging

N X

THERMO-ABLATION
(micro-onde): FOIE

EN COURS



N 1

THERMO-ABLATION

PROGRESSION GLOBALE

FOLFOX

H0 H2 H24 J 8 J 30 J 63

Mutation 1: KRAS (NM_033360.3) p.Gly12Ala c.35G>C

0 0 1,8% 0,90% 1%

Mutation 2: TP53 (NM_000546.5) p.Leu130Val c.388C>G

0 0 0 5%? 3,3%

ADN

0,75 1,19 0,20 0,10 0,1

N 2

THERMO-ABLATION

Imagerie J90:
PAS DE PROGRESSION

H0 | H2 | H24 | J 30

Mutation 1: TP53 (NM_000546.5) p.Arg248Trp c.742C>T

1% | 2,3% | 1,4% | 0,6% | 0,2%

Mutation 2: TP53 (NM_000546.5) p.Arg158His c.473G>A

0 | 2,1% | 1,2% | 0,1% | 0,2%

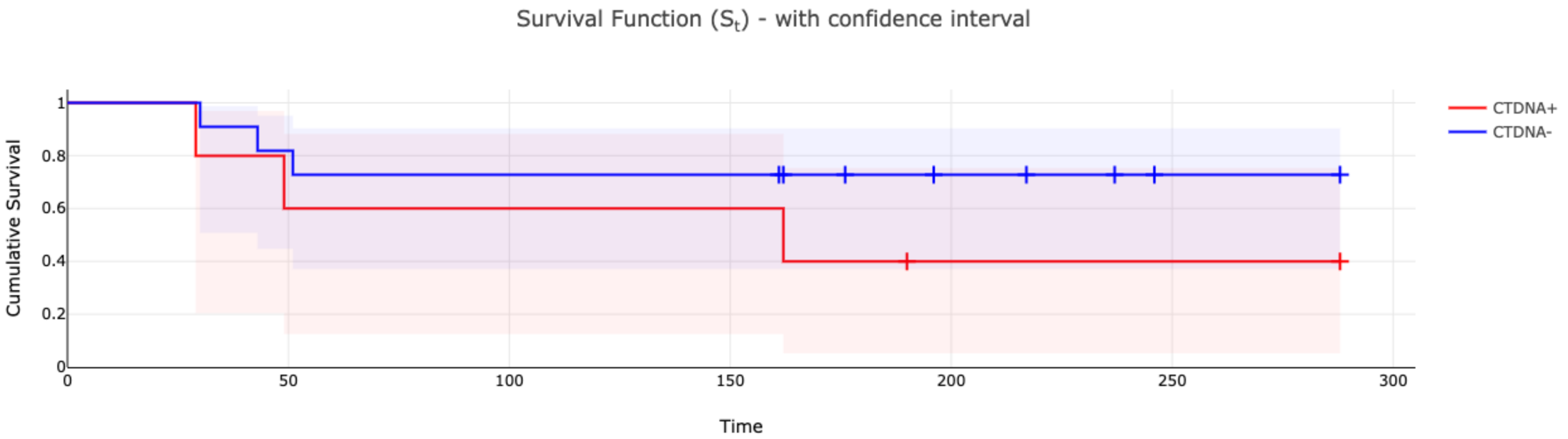
ADN

0,3 | 0,7 | 4,52 | 0,13 | 0,3

16 patients en “intent-to-cure”

5 ADNtc + pré-opératoires : 3 progressions, 2 non progressions (60%)
11 ADNtc – pré-opératoires: 3 progressions, 8 non progressions (27%)

TP53 (NM_000546.5) p.Arg248Trp c.742C>T	1%
KRAS (NM_033360.3) p.Gly12Asp c.35G>A	5%
KRAS (NM_033360.3) p.Gly12Val c.35G>T	4%
SMAD4 (NM_005359.5) p.Ser343Leu c.1028C>T	1%
KRAS (NM_033360.3) p.Gly12Ser c.34G>A	14%


Survival Function (S_t) - with confidence interval
Cumulative Survival
1
0.8
0.6
0.4
0.2
0
0
50
100
150
200
250
300
Time
CTDNA+
CTDNA-

Limites

Recurrence-free survival versus overall survival as a primary endpoint for studies of resected colorectal liver metastasis: a retrospective study and meta-analysis

Brett L Ecker, Jasme Lee*, Lily V Saadat, Thomas Aparicio, Florian E Buisman, Vinod P Balachandran, Jeffrey A Drebin, Kiyoshi Hasegawa, William R Jarnagin, Nancy E Kemeny, T Peter Kingham, Bas Groot Koerkamp, Norihiro Kokudo, Yutaka Matsuyama, Guillaume Portier, Leonard B Saltz, Kevin C Soares, Alice C Wei, Mithat Gonen†, Michael I D'Angelica†*

« A surrogate endpoint is a ***substitute*** of a primary end point expected to predict the clinical benefit, harm, or absence of an intervention »

« For the postsurgical management of patients with colorectal liver metastases, **all randomised** controlled trials to date assessing the clinical value of adjuvant chemotherapy have used recurrence-free survival as the primary endpoint.»

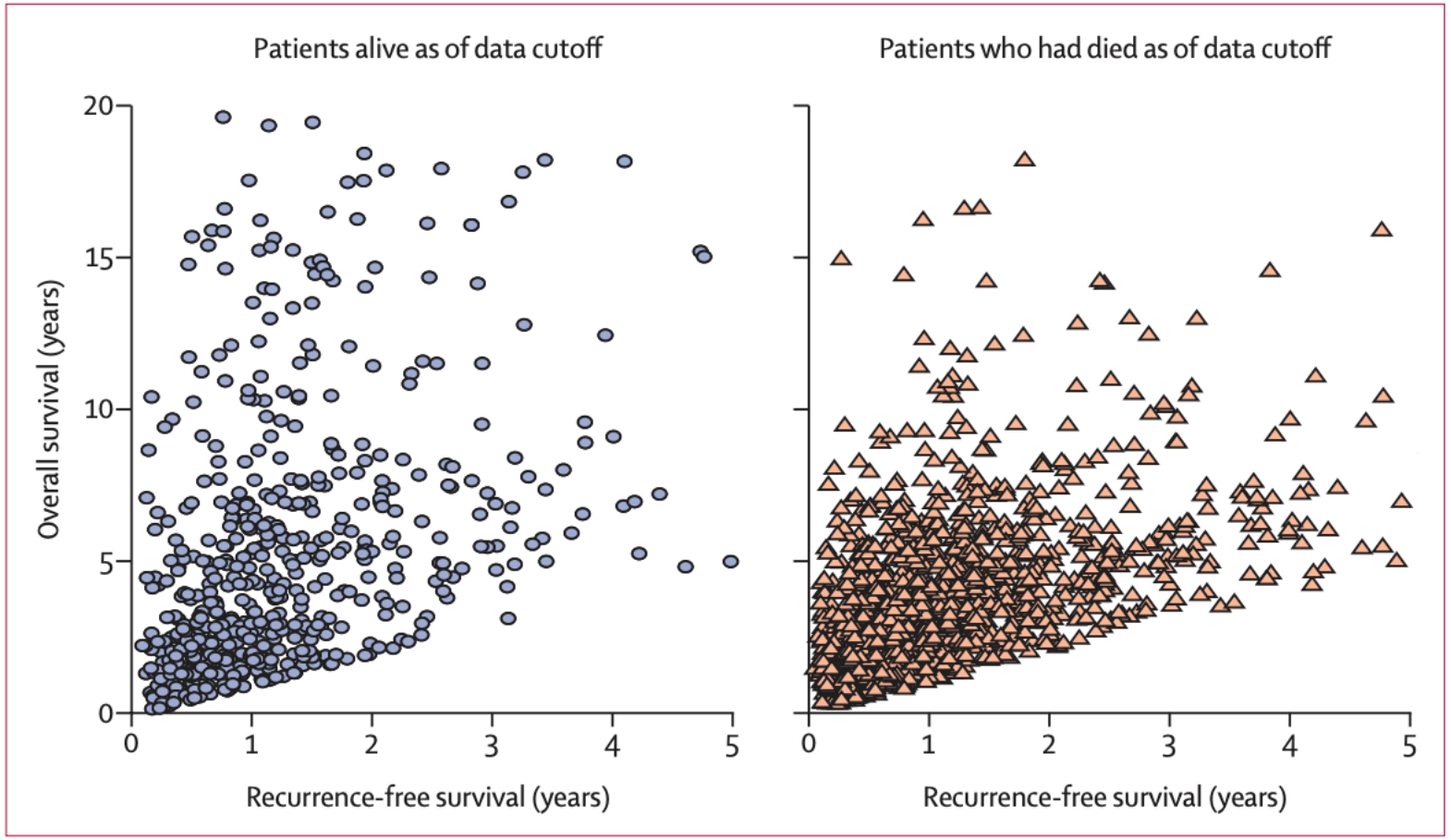


Figure 1: **Scatterplot of overall survival versus recurrence-free survival for patients with recurrence (n=1995) in the resected colorectal liver metastasis cohort**

Data are shown by vital status at data cutoff (Sept 15, 2019). Only data for recurrence-free survival of 5 years or less and overall survival of 20 years or less are shown.

we provide evidence that the **correlation** between recurrence-free survival and overall survival in this disease context is **minimal...**

Recurrence-free survival is an ***inadequate surrogate for overall survival***

	2-year overall survival	3-year overall survival	4-year overall survival	5-year overall survival	6-year overall survival	7-year overall survival	8-year overall survival	9-year overall survival	10-year overall survival
1-year recurrence-free survival	0·37 (0·16)	0·42 (0·16)	0·42 (0·16)	0·40 (0·16)	0·38 (0·17)	0·37 (0·16)	0·33 (0·17)	0·31 (0·17)	0·30 (0·17)
2-year recurrence-free survival	..	0·40 (0·16)	0·44 (0·16)	0·46 (0·16)	0·47 (0·16)	0·46 (0·16)	0·44 (0·16)	0·42 (0·16)	0·40 (0·16)
3-year recurrence-free survival	..	..	0·44 (0·16)	0·49 (0·15)	0·51 (0·15)	0·51 (0·15)	0·49 (0·15)	0·48 (0·15)	0·46 (0·15)
4-year recurrence-free survival	..	..	..	0·49 (0·15)	0·52 (0·14)	0·54 (0·14)	0·52 (0·14)	0·52 (0·14)	0·51 (0·14)
5-year recurrence-free survival	..	..	..	..	0·54 (0·13)	0·56 (0·13)	0·55 (0·13)	0·55 (0·13)	0·54 (0·14)

Data are mean (SD). Estimates are calculated from 1000 random sample runs, and at each sample run, correlations of overall survival and recurrence-free survival probabilities at the specified time pairs were estimated for 30 randomly assigned groups.

Table 2: **Pairwise Spearman's correlation estimates of overall survival versus recurrence-free survival in the resected colorectal liver metastasis cohort**

« time to recurrence did not reliably predict the survival outcome »

Merci!