

CBNPC oligométastatique

Définition et prise en charge

Cours du GOLF 2019 - Toulouse



Jonathan Khalifa

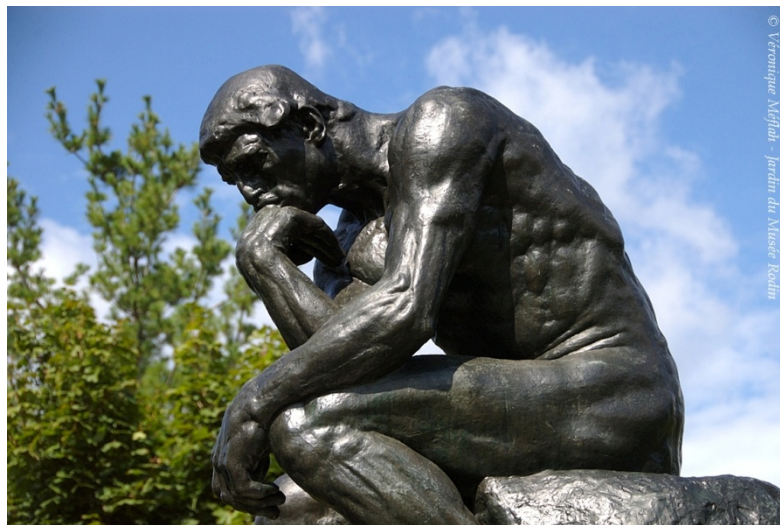
Radiothérapie

Institut Universitaire du Cancer de Toulouse – Oncopole

 [@jnt_khalifa](https://twitter.com/jnt_khalifa)

La maladie « oligométastatique »

Nouveau paradigme en cancérologie ...



La maladie « oligométastatique »

THE RESULTS OF OPERATIONS FOR THE CURE OF
CANCER OF THE BREAST PERFORMED AT
THE JOHNS HOPKINS HOSPITAL
FROM JUNE, 1889, TO JANU-
ARY, 1894.

By WILLIAM¹ S. HALSTED, M.D.,

OF BALTIMORE,

PROFESSOR OF SURGERY IN JOHNS HOPKINS UNIVERSITY.

vs

[CANCER RESEARCH 40, 3863-3874, November 1980]
0008-5472/80/0040-0000\$02.00

Laboratory and Clinical Research in Breast Cancer—A Personal Adventure:
The David A. Karnofsky Memorial Lecture¹

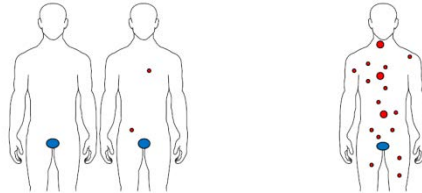
Bernard Fisher²

University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15261

Cancer = maladie graduelle
 $T \rightarrow N \rightarrow M$

Cancer = maladie systémique d'emblée
Micrométastatique

« Spectrum theory »



Etat oligométastatique



La maladie « oligométastatique »

Un concept clinique

INTERNATIONAL JOURNAL OF ONCOLOGY 25: 1677-1683, 2004

Analysis of further disease progression in metastatic non-small cell lung cancer: Implications for locoregional treatment

NEIL MEHTA¹, ANN M. MAUER^{2,3}, SAMUEL HELLMAN¹, DANIEL J. HARAF^{1,3}, EZRA E. W. COHEN²,
EVERETT E. VOKES^{1,2,3} and RALPH R. WEICHELBAUM^{1,3}

- **Patients longs survivants**
- **Intervalle libre long à la récurrence**
- **Récurrence préférentielle au niveau des sites oligo-métastatiques**

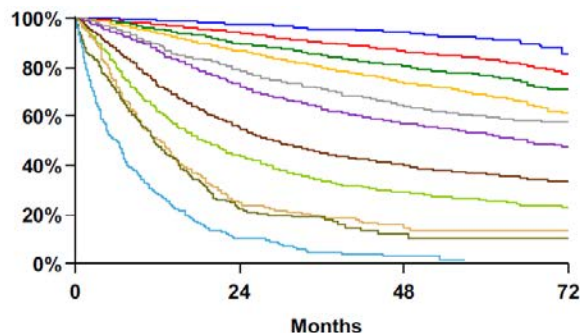


La maladie « oligométastatique »

Un concept clinique

The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer

Peter Goldstraw, FRCS,^{a,*} Kari Chansky, MS,^b John Crowley, PhD,^b Ramon Rami-Porta, MD,^c Hisao Asamura, MD,^d Wilfried E. E. Eberhardt, MD,^e Andrew G. Nicholson, FRCP,^f Patti Groome, PhD,^g Alan Mitchell, MS,^b Vanessa Bolejack, MPH,^b on behalf of the International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee, Advisory Boards, and Participating Institutions



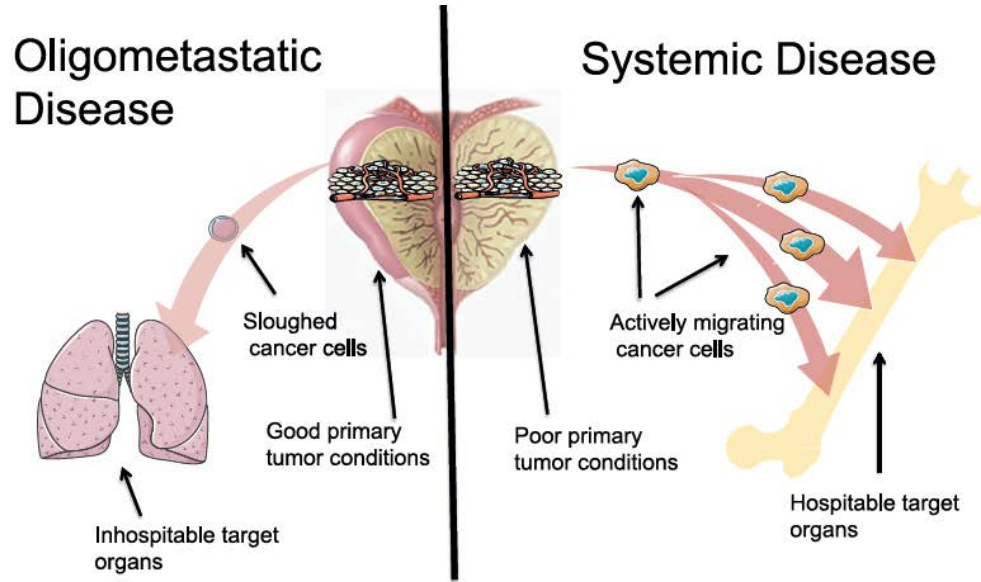
Proposed	Events / N	MST	24 Month	60 Month
IA1	68 / 781	NR	97%	92%
IA2	505 / 3105	NR	94%	83%
IA3	546 / 2417	NR	90%	77%
IB	560 / 1928	NR	87%	68%
IIA	215 / 585	NR	79%	60%
IIB	605 / 1453	66.0	72%	53%
IIIA	2052 / 3200	29.3	55%	36%
IIIB	1551 / 2140	19.0	44%	26%
IIIC	831 / 986	12.6	24%	13%
IVA	336 / 484	11.5	23%	10%
IVB	328 / 398	6.0	10%	0%

M1	Distant metastasis present
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion ^d
M1b	Single extrathoracic metastasis ^e
M1c	Multiple extrathoracic metastases in one or more organs



La maladie « oligométastatique »

Une réalité biologique



La maladie « oligométastatique »

Une réalité biologique

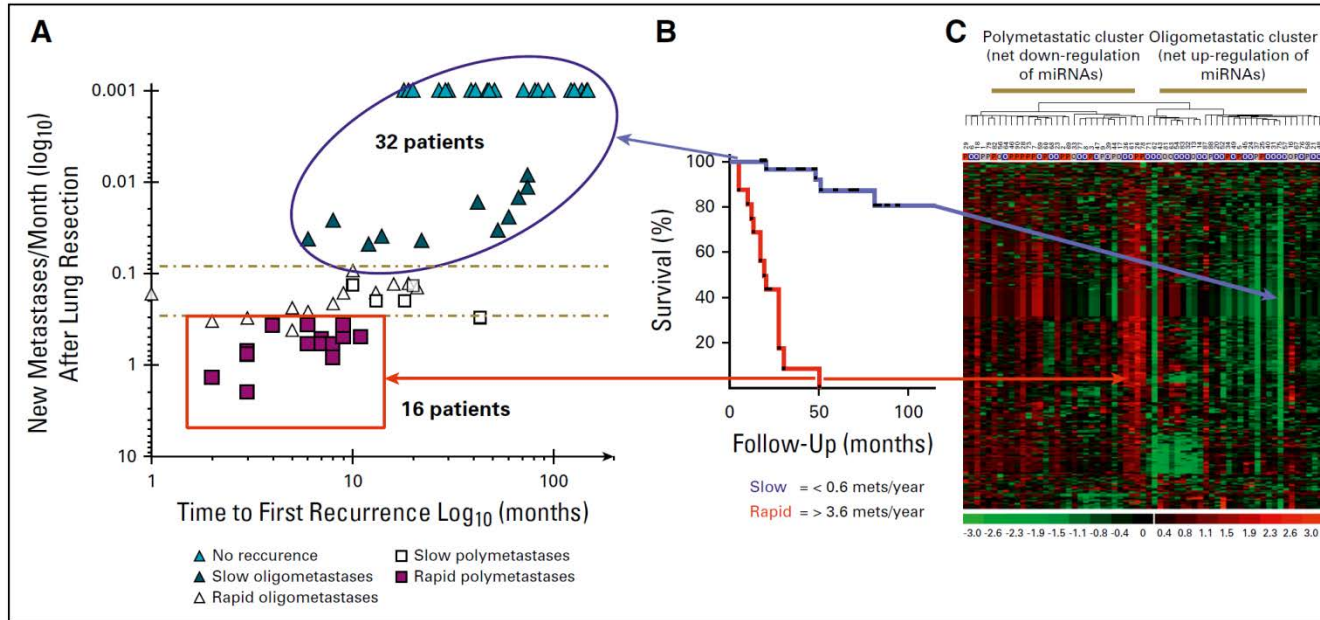


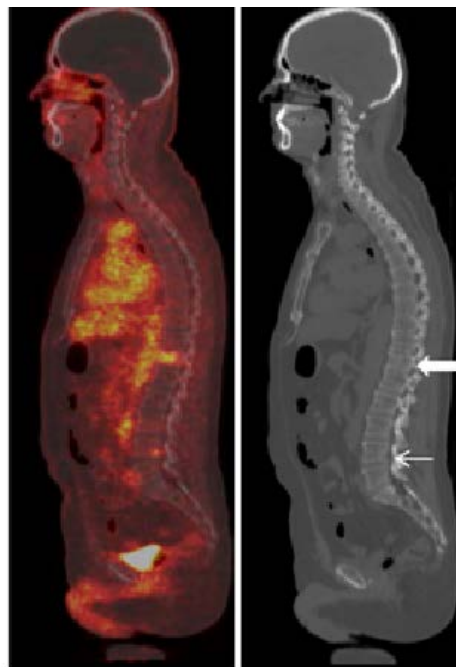
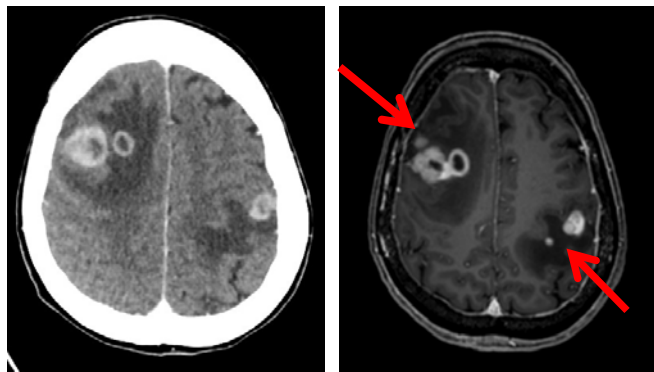
Fig 1. Oligo- and polymetastatic progression in patients with lung metastases (mets) is associated with specific microRNAs (miRNAs). (A) Graph of time to recurrence of new metastasis after resection of pulmonary metastasis. The circle represents the slow progressors (< 0.6 metastases/year) with a good prognosis as indicated in (B), whereas the square in the lower left of (A) represents rapid progressors (> 3.6 metastases/year) characterized by a poor prognosis, as indicated (B). (B) Survival as a function of time to recurrence. (C) Differentially expressed miRNAs associated with (B) survival and (A) time to recurrence of rapid and slow progressors. Adapted with permission.¹⁹



La maladie « oligométastatique »

Quelle définition ?

- Nombre de métastases ?



La maladie « oligométastatique »

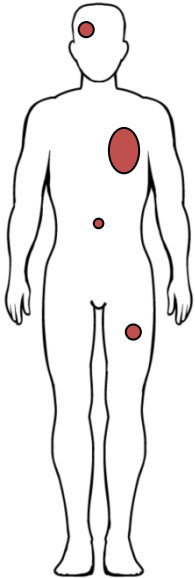
Quelle définition ?

- Nombre de métastases ?
- Volume lésionnel total ?
- Nombre d'organes atteints ?
- Histologie ?
- Chronologie ?



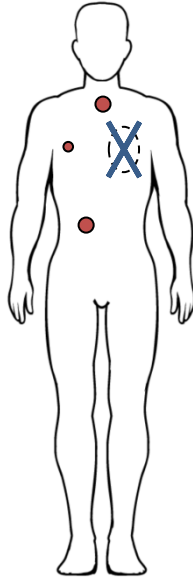
Les maladies « oligométastatiques »

Maladie oligométastatique synchrone



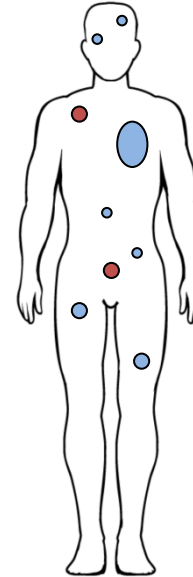
Nombre limité de métastases
au diagnostic

Oligorécidive



Apparition d'un nombre limité de métastases
à distance du traitement radical du primitif

Oligoprogression



Métastases multiples au diagnostic

Réponse initiale au traitement systémique

Progression d'un nombre limité de métastases
sous ou après arrêt du traitement systémique



Vers un consensus ...?



Journal of Thoracic Oncology

Available online 6 August 2019

In Press, Journal Pre-proof



Original Article

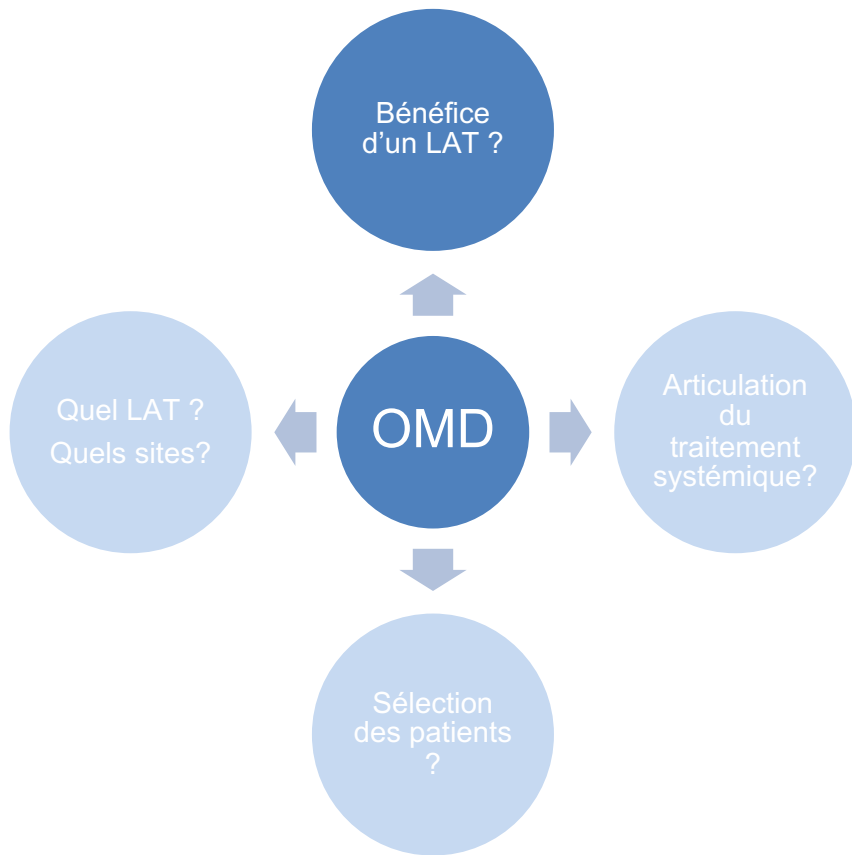
Definition of **synchronous** oligo-metastatic non-small cell lung cancer – a consensus report

Anne-Marie C. Dingemans^{1,2,3,4}, Lizza E.L. Hendriks¹, Thierry Berghmans MD, PhD³, Antonin Levy MD⁴, Baktiar Hasan⁵, Corinne Faivre-Finn⁶, Matteo Gajaj-Levra⁷, Niccolò Gajaj-Levra⁸, Nicolas Girard⁹, Laurent Greillier¹⁰, Sylvie Lantuéjoul¹¹, John Edwards¹², Mary O'Brien¹³, Martin Reck¹⁴, Egbert F. Smit¹⁵, Paul Van Schil¹⁶, Pieter E. Postmus¹⁷, Sara Ramella¹⁸ ... Silvia Novello²²

Consensus questions	Statement
AIM OF TREATMENT sOM-NSCLC	
1.1, 2.1, 2.2	Definition of sOM-NSCLC is relevant when a radical treatment is technically feasible with acceptable toxicity, with all sites being amenable to local treatment modality, that may modify the course of the disease and be considered as an opportunity for long-term disease control.
DEFINITION OF sOM-NSCLC	
2.3	As the definition is not determined by the type of radical treatment (only its feasibility), histology and genomic background are not taken into account in this definition.
2.4, 2.5, 2.6	The maximum number of metastases/organs involved depends on the possibility of offering a radical intent treatment strategy. Based on the systematic review, a maximum of 5 metastases and 3 organs is proposed. The presence of diffuse serosal metastases or bone marrow involvement excludes cases from this definition.
2.7, 2.12	Use of risk classification groups or total tumor volume is of interest, but that there is a lack of data to formulate a statement
2.8, 2.9	All organs are allowed, except diffuse serosal metastases (meningeal, pericardial, pleural, mesenteric) as well as bone marrow involvement as these cannot be treated with radical intent.
2.10	Pulmonary metastases are counted as a metastatic site.
2.11	Mediastinal lymph nodes should not count as a metastatic site; mediastinal lymph nodes must be considered as regional disease. However, mediastinal lymph node involvement is of importance in determining if radical local treatment of the primary may be applied.
STAGING OF sOM-NSCLC	
3.1, 3.2	¹⁸F-FDG-PET-CT and brain imaging are mandatory. For brain imaging, MRI is preferred.
3.3	Mediastinal staging with ¹⁸ F-FDG-PET-CT is needed, with pathological confirmation required if this influences treatment strategy.
3.4, 3.5	Pathological confirmation of at least one metastasis is required unless the MDT decides that the risk outweighs the benefit.
3.5	In addition to sections 3.2-3.3, for a solitary metastasis on ¹⁸ F-FDG-PET, in specific cases additional work-up is advised. When the liver is the only site of oligometastatic disease a dedicated MRI of the liver is advised , and if a solitary pleural metastasis is suspected on imaging, then thoracoscopy and dedicated biopsies of other ipsilateral pleural sites are recommended as multifocal disease is often evidenced in this context during procedure.

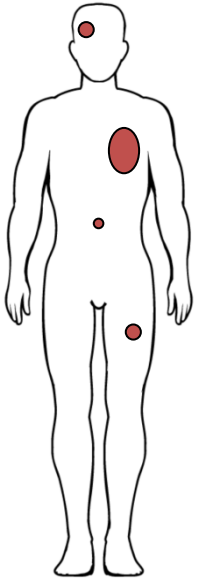


Problématiques de la gestion des OMD



Bénéfice d'un LAT ?

Maladie oligométastatique synchrone



Nombre limité de
métastases
au diagnostic

Hypothèse :

Traitement ablatif de **tous les sites (T/M)**
(= traitement de consolidation post CT)
→ **augmente la survie ?**



Bénéfice d'un LAT ?

Maladie oligométastatique synchrone

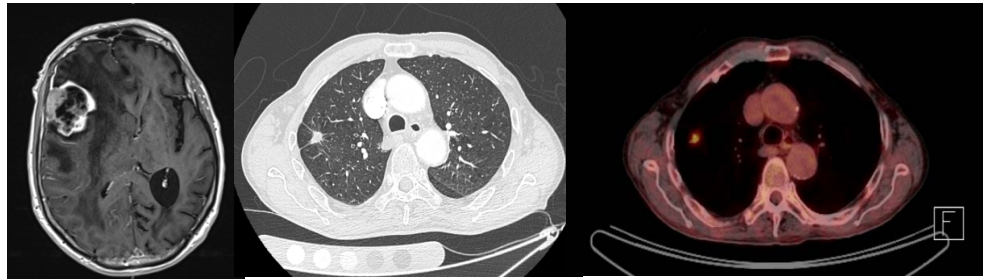
Mr S. 73 ans

Pas d'antécédents notables

Tabac : 50 PA sevré depuis 3 ans

HDM:

Crise comitiale



Avril 2017

→ Chirurgie de la lésion frontale :
ADK T1bN0M1b PDL1 10% (NRas muté en NGS)



Bénéfice d'un LAT ?

Maladie oligométastatique
synchrone



Avril 2017 Mai 2017

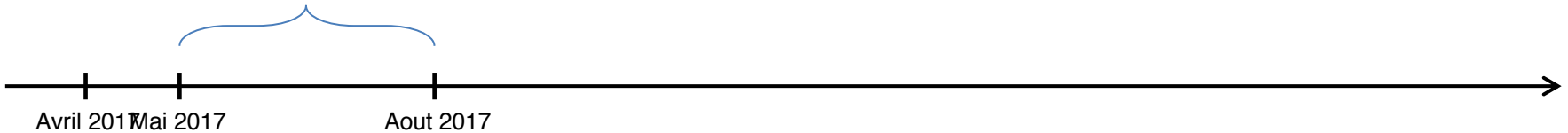
ADK T1bN0M1b PDL1 10% (NRas muté en NGS)



Bénéfice d'un LAT ?

Maladie oligométastatique
synchrone

Chimio : CDDP-Nvl x5

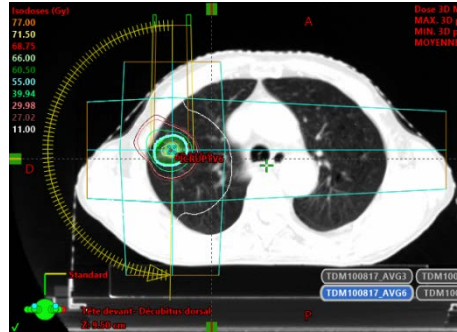


ADK T1bN0M1b PDL1 10% (NRas muté en NGS)



Bénéfice d'un LAT ?

Maladie oligométastatique
synchrone



Avril 2017

Sept 2017

ADK T1bN0M1b PDL1 10% (NRas muté en NGS)

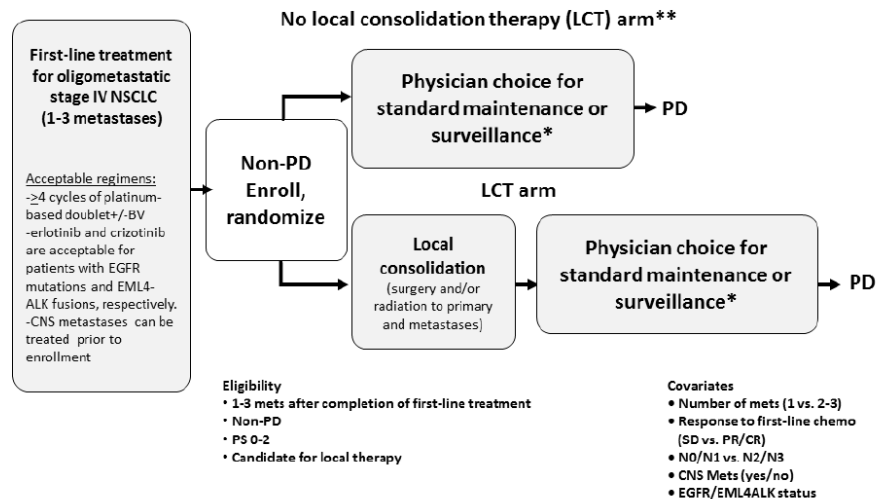


Bénéfice d'un LAT ?

Maladie oligométastatique synchrone

Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study

Daniel R Gomez, George R Blumenschein Jr, Jack Lee, Mike Hernandez, Rong Ye, D Ross Camidge, Robert C Doebbele, Ferdinando Skoulidis, Laurie E Gaspar, Don L Gibbons, Jose A Karam, Brian D Kavanagh, Chad Tang, Ritsuko Komaki, Alexander V Louie, David A Palma, Anne S Tsao, Boris Sepesi, William N William, Jianjun Zhang, Qiuling Shi, Xin Shelley Wang, Stephen G Swisher, John V Heymach**



	Local consolidative therapy (n=25)	Maintenance treatment (n=24)
Age		
Mean (SD)	64 (10)	63 (10)
Median (IQR)	63 (43-83)	61 (43-80)
Sex		
Male	12 (48%)	10 (42%)
Female	13 (52%)	14 (58%)
Ethnicity		
White	20 (80%)	18 (75%)
Black	2 (8%)	3 (12%)
Hispanic	2 (8%)	0
Asian	1 (4%)	3 (12%)
Tumour histology		
Adenocarcinoma	21 (84%)	18 (75%)
Adenosquamous	0	1 (4%)
NSCLC, NOS	1 (4%)	0
Poorly differentiated NSCLC, NOS	2 (8%)	0
SCC	1 (4%)	4 (17%)
Sarcomatoid carcinoma	0	1 (4%)
Time of metastases		
Metachronous	1 (4%)	2 (8%)
Synchronous	24 (96%)	22 (92%)
Non-regional metastases after first-line systemic therapy		
0-1	17 (68)	15 (62)
2-3	8 (32)	9 (38)
Response to first-line chemotherapy		
Partial response or complete response	9 (36%)	9 (38%)
Stable disease	16 (64%)	15 (62%)
CNS metastases		
No	18 (72%)	18 (75%)
Yes	7 (28%)	6 (25%)
Nodal status		
N0/N1	12 (48%)	11 (46%)
N2/N3	13 (52%)	13 (54%)
Mutation type		
None	20 (80%)	21 (88%)
EGFR	3 (12%)	3 (12%)
EML4ALK	2 (8%)	0

Bénéfice d'un LAT ?

Maladie oligométastatique synchrone

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Follow-up : 38.8 mois

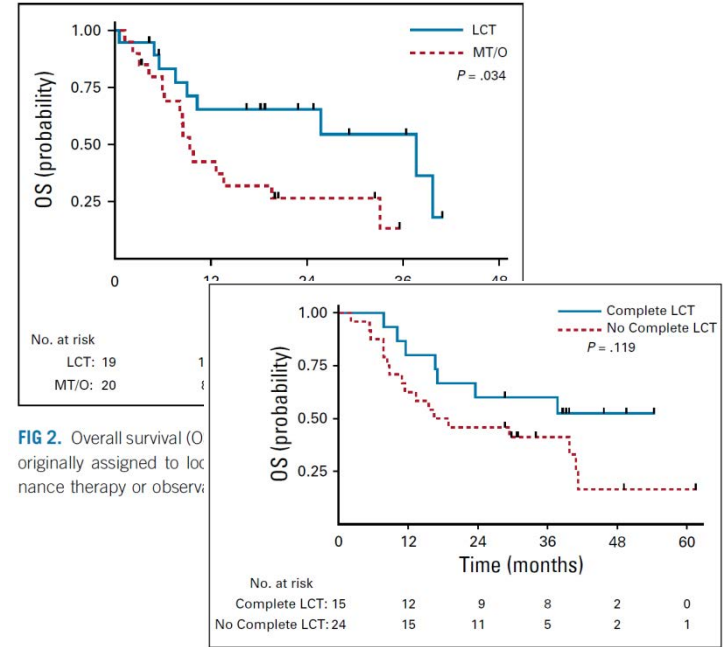
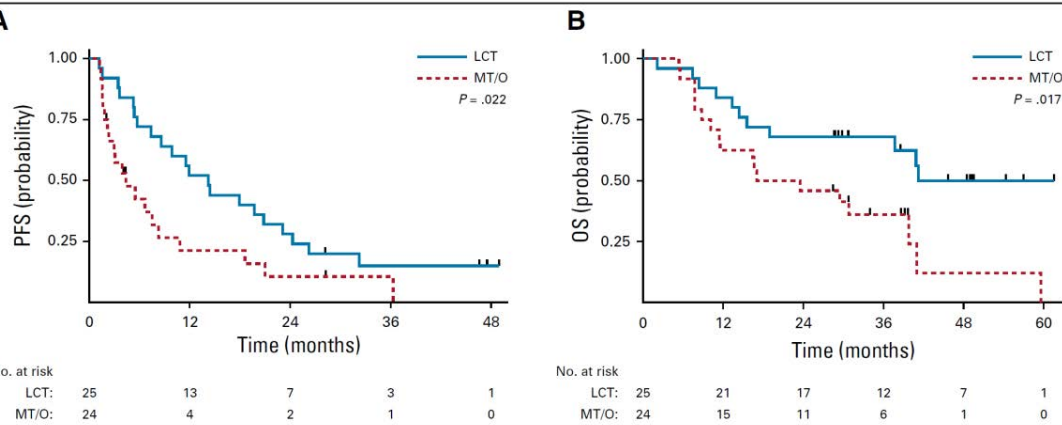


FIG 3. Overall survival (OS) from time of progression, for patients who did or did not receive late local consolidation therapy (LCT) for that progression. "Complete" LCT designates radiation therapy or surgery to all active sites of disease at the time of progression.

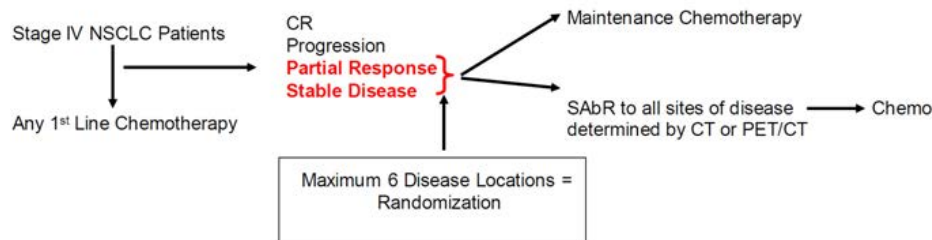
Bénéfice d'un LAT ?

Maladie oligométastatique synchrone

JAMA Oncology | Original Investigation

Consolidative Radiotherapy for Limited Metastatic Non-Small-Cell Lung Cancer A Phase 2 Randomized Clinical Trial

Puneeth Iyengar, MD, PhD; Zabi Wardak, MD; David E. Gerber, MD; Vasu Tumati, MD; Chul Ahn, PhD; Randall S. Hughes, MD; Jonathan E. Dowell, MD; Naga Cheedella, MD; Lucien Nedzi, MD; Kenneth D. Westover, MD, PhD; Suprabha Pulipparacharuvil, PhD; Hak Choy, MD; Robert D. Timmerman, MD

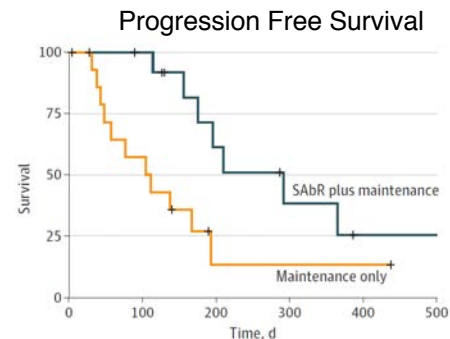


Primary End Point – PFS

Secondary End Points – OS, Toxicity, Patterns of Failure

All metastatic sites and primaries were treated with SABr if feasible. Central primary disease and mediastinal LN metastases were treated with either SABr or hypofractionated radiation (45Gy in 15Fx).

Characteristic	No. (%)		P Value
	SABr Plus Maintenance	Maintenance Only	
Sex			.70
Male	9 (64.3)	11 (73.3)	
Female	5 (35.7)	4 (26.7)	
Median (range) age, y	63.5 (51.0-78.0)	70.0 (51.0-79.0)	.13
Histology			.61
Squamous	1 (7.1)	3 (20.0)	
Nonsquamous	13 (92.9)	12 (80.0)	
Sites of disease prior to induction chemotherapy, median No. (range)	3 (2-6)	2 (2-5)	.58
Previously treated brain metastases			.61
Yes	6 (42.9)	5 (33.3)	
No	8 (57.1)	10 (66.7)	
Induction chemotherapy, median cycles (range)	4.5 (4-6)	4 (4-6)	.31

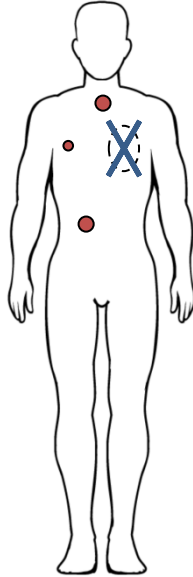


No. at risk	0	100	200	300	400	500
SABr plus maintenance	14	12	6	3	1	
Maintenance only	15	8	1	1	1	



Bénéfice d'un LAT ?

Oligorécidive



Apparition d'un nombre limité de métastases à distance du traitement radical du primitif

Hypothèse :

Traitement ablatif de **tous les sites M**
→ **retarde l'introduction du ttt systémique ?**
→ **et/ou augmente la survie** (associé au ttt syst)?



Bénéfice d'un LAT ?

Oligorécidive

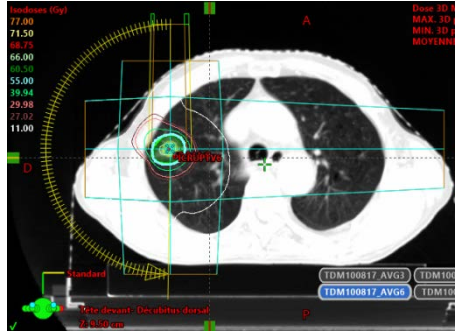
Mr S. 73 ans

Pas d'antécédents notables

Tabac : 50 PA sevré depuis 3 ans

HDM:

Crise comitiale



Avril 2017

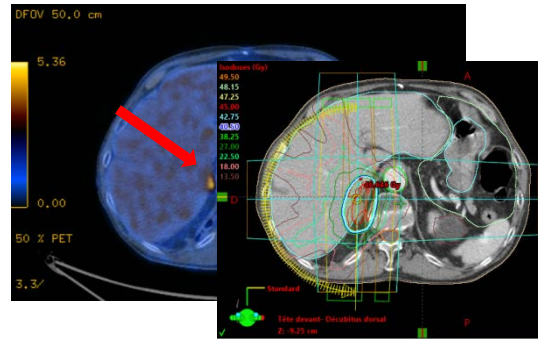
Sept 2017

ADK T1bN0M1b PDL1 10% (NRas muté en NGS)



Bénéfice d'un LAT ?

Oligorécidive



Avril 2017

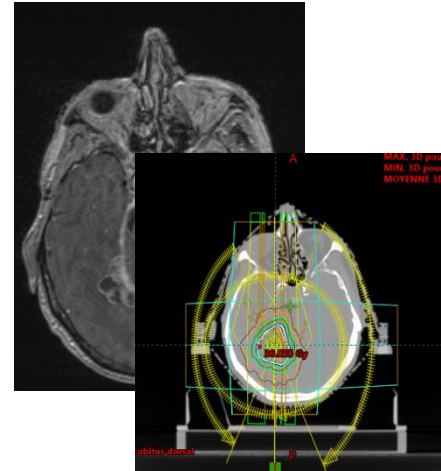
Février 2018

ADK T1bN0M1b PDL1 10% (NRas muté en NGS)



Bénéfice d'un LAT ?

Oligorécidive



Avril 2017

Sept 2018

ADK T1bN0M1b PDL1 10% (NRas muté en NGS)



Bénéfice d'un LAT ?

Oligorécidive

Non évolutif à près de 2 ans et ½ du primo-diagnostic

Primitif contrôlé

Pas de reprise de traitement systémique malgré 2 évènements évolutifs survenus à respectivement 5 et 12 mois de la fin de la 1^{ère} séquence thérapeutique

Dernier intervalle libre : 1 an

Avril 2017

Septembre 2019

ADK T1bN0M1b PDL1 10% (NRas muté en NGS)

Non évolutif



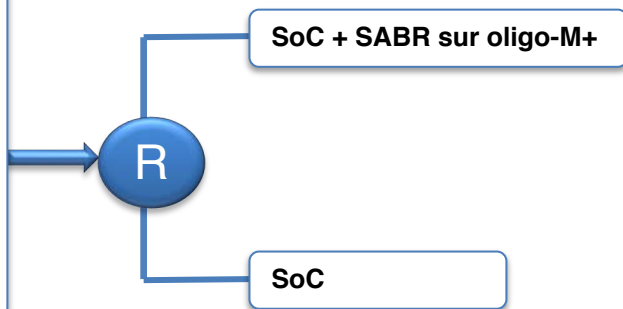
Bénéfice d'un LAT ?

Oligorécidive

Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial

David A Palma, Robert Olson, Stephen Harrow, Stewart Gaede, Alexander V Louie, Cornelis Haasbeek, Liam Mulroy, Michael Lock, George B Rodrigues, Brian P Yaremko, Devin Schellenberg, Belal Ahmad, Gwendolyn Griffioen, Sashendra Senthil, Anand Swaminath, Neil Kopek, Mitchell Liu, Karen Moore, Suzanne Currie, Glenn S Bauman, Andrew Warner, Suresh Senan

- Toute tumeur solide
- Primitif contrôlé (ttt radical > 3 mois, absence de récurrence locale)
- Pas de ttt systémique durant les 4 dernières semaines (sauf HT = autorisée)
- Oligométastatique :
 - ≤ 5 M+
 - ≤ 3M+ dans le même organe



CJP : OS

	Control group (n=33)	SABR group (n=66)
Age	69 (64-75)	67 (59-74)
Sex		
Men	19 (58%)	40 (61%)
Women	14 (42%)	26 (39%)
Site of original primary tumour		
Breast	5 (15%)	13 (20%)
Colorectal	9 (27%)	9 (14%)
Lung	6 (18%)	12 (18%)
Prostate	2 (6%)	14 (21%)
Other	11 (33%)	18 (27%)
Time from diagnosis of primary tumour to randomisation (years)	2.3 (1.3-4.5)	2.4 (1.6-5.3)
Number of metastases		
1	12 (36%)	30 (46%)
2	13 (40%)	19 (29%)
3	6 (18%)	12 (18%)
4	2 (6%)	2 (3%)
5	0 (0%)	3 (5%)
Location of metastases		
Adrenal	2/64 (3%)	7/127 (6%)
Bone	20/64 (31%)	45/127 (35%)
Liver	3/64 (5%)	16/127 (13%)
Lung	34/64 (53%)	55/127 (43%)
Other*	5/64 (8%)	4/127 (3%)

Data are n (%), n/N (%), or median (IQR). SABR=stereotactic ablative radiotherapy. *Other comprises brain (n=3 lesions in control group; n=1 lesion in SABR group), lymph nodes (n=1 lesion in control group; n=3 lesions in SABR group), and para-renal (n=1 lesion in control group).

Table 1: Baseline characteristics

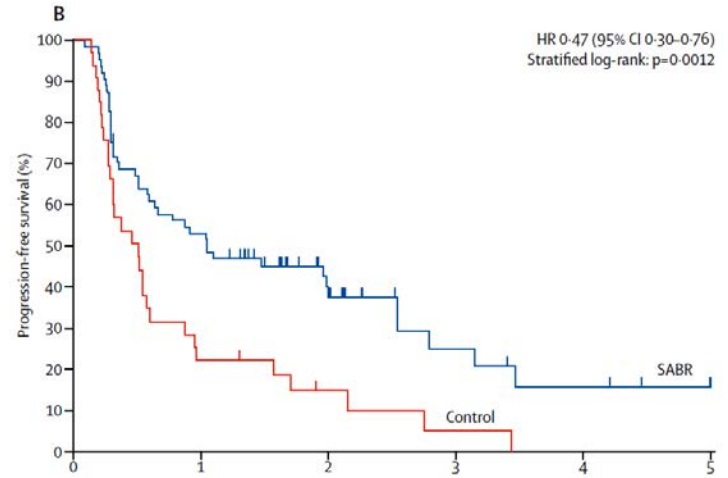
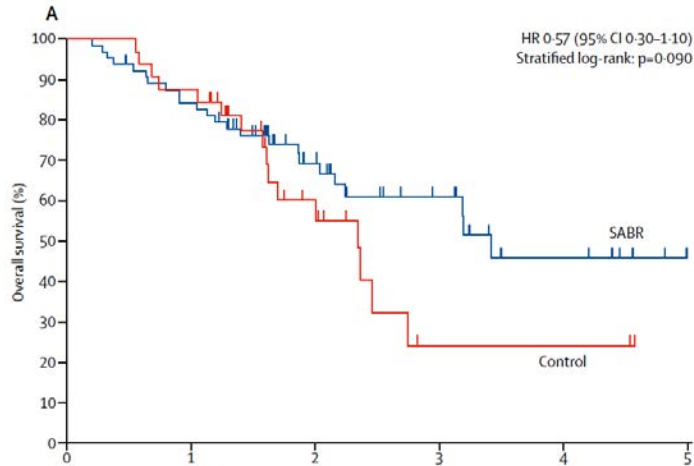


Bénéfice d'un LAT ?

Oligorécidive

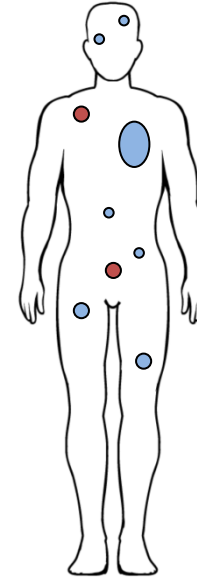
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Bénéfice d'un LAT ?

Oligoprogression



Métastases multiples au diagnostic

Réponse initiale au traitement systémique

Progression d'un nombre limité de métastases *sous ou après arrêt du traitement systémique*

Hypothèse :

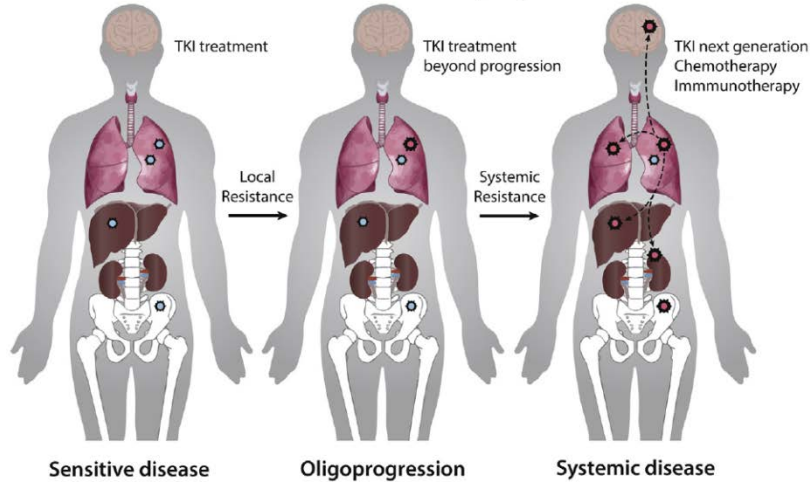
Traitement ablatif de **tous les sites progressifs**
→ retarde le changement de traitement syst ?
→ et/ou augmente la survie



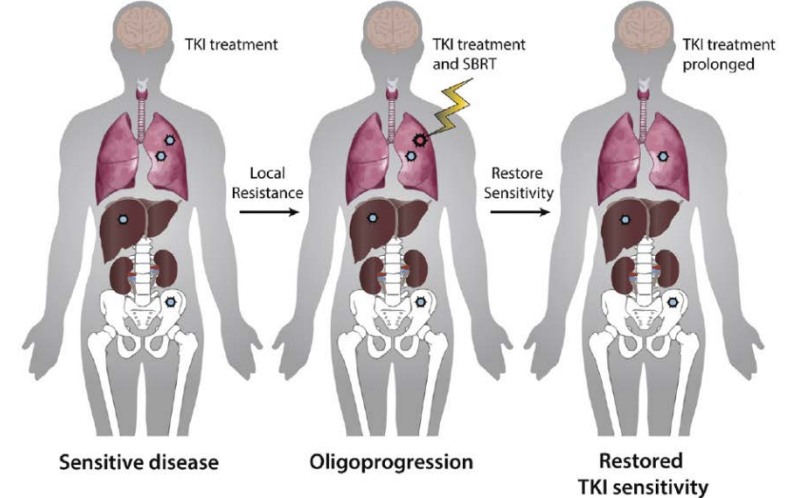
Bénéfice d'un LAT ?

Oligoprogression

Natural course of disease progression



Local irradiation to eradicate oligoresistant disease



Bénéfice d'un LAT ?

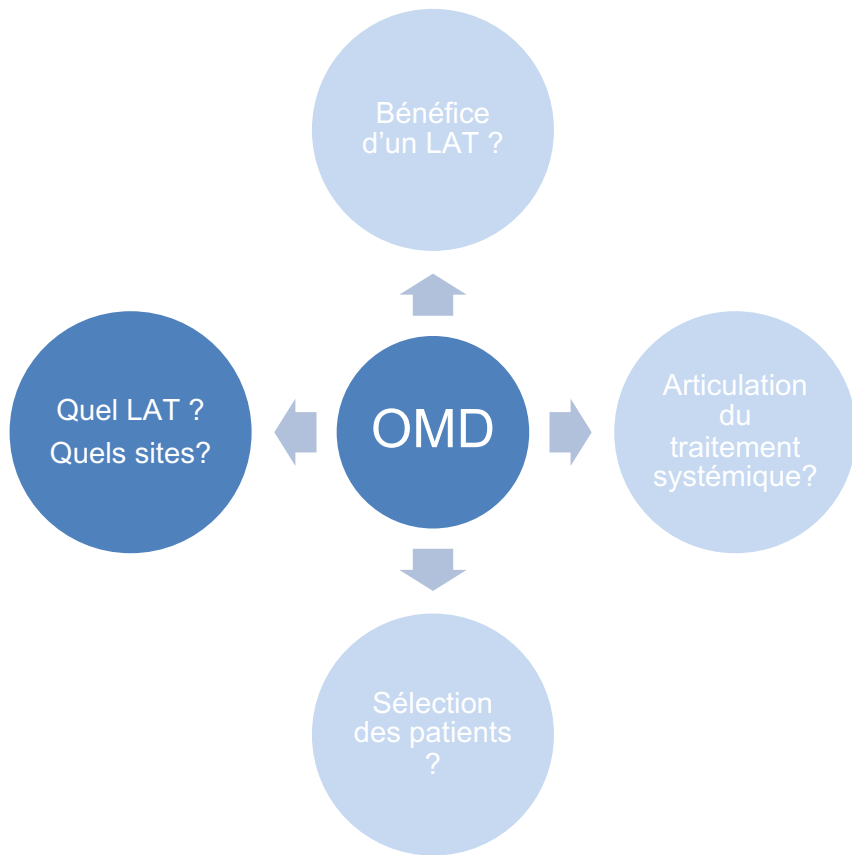
Oligoprogression

Prospective clinical trials involving aggressive local treatment in the setting of targeted therapy and oligoprogressive disease (OPD).

Trial	Tumor entity	Criteria	Study design	Intervention	Primary outcome
NCT02019576	Renal Cell Carcinoma	Oligoprogression in patients receiving	Single arm phase II, multi-center	SBRT	Local control
NCT01941654	NSCLC (EGFR mutated)	1st line Sunitinib therapy 1st line TKI treatment for at least 3 months with CT-confirmed good partial response. ≤ 4 PET-positive residual tumor sites	Single arm phase II	SBRT	PFS at 1 year
NCT01573702	NSCLC (EGFR mutated)	Oligoprogression in patients following EGFR-TKI treatment. ≤5 OPD sites (intra and extra-cranial)	Single arm phase II	SBRT or other local ablation followed by Erlotinib	PFS
NCT02450591	NSCLC (EGFR mutated)	Completion of 12 weeks Erlotinib treatment. ≤5 disease sites at time of diagnosis, all amenable to definitive local therapy.	Single arm pilot study	SBRT, surgery or other local ablation to all remaining sites of disease	Feasibility
NCT01796288	NSCLC (EGFR mutated)	12 weeks of second-line Erlotinib without disease progression. ≤5 disease sites	Randomized phase II	RT to all gross tumor sites + Erlotinib vs. Erlotinib alone	PFS
HALT	NSCLC (EGFR/ALK mutated)	Confirmed response to TKI therapy after a treatment time of 2–3 months. ≤3 OPD sites (extra-cranial), all suitable for treatment with SBRT	Randomized phase II/III, multi-center	SBRT in addition to TKI therapy vs. TKI therapy alone	PFS



Problématiques de la gestion des OMD



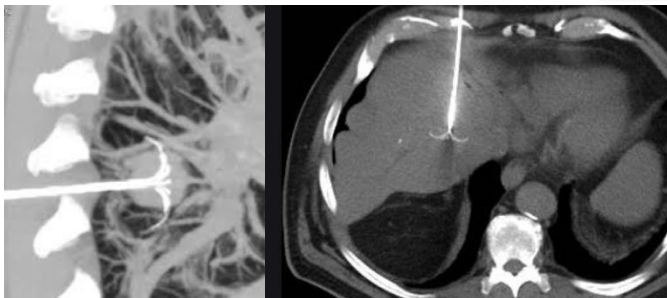
Quel LAT pour quels sites ?

SBRT

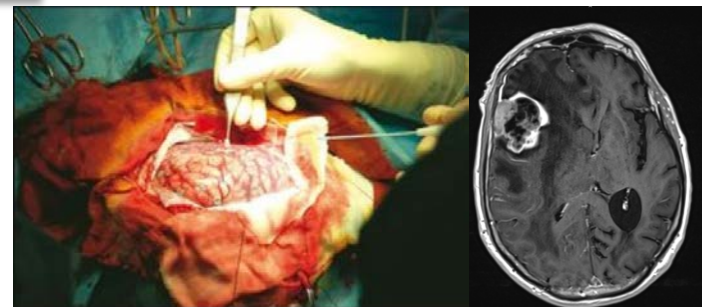


Etat du patient
Nombre/taille des lésions
Morbidité du geste
Résécabilité/accessibilité tt percutané
Possibilité de respecter les contraintes de doses
Urgence décompressive
Choix du patient...

Radiologie interventionnelle



Chirurgie

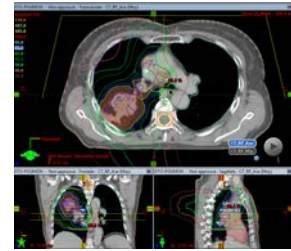
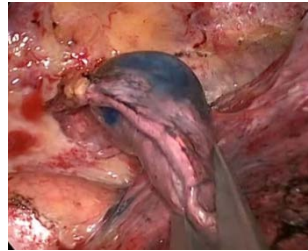
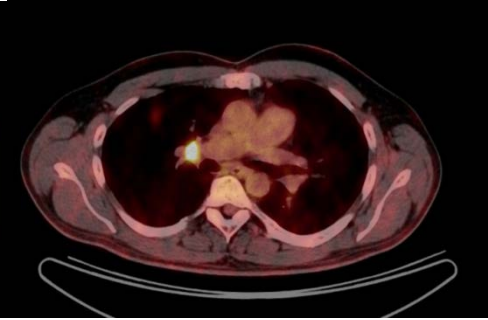
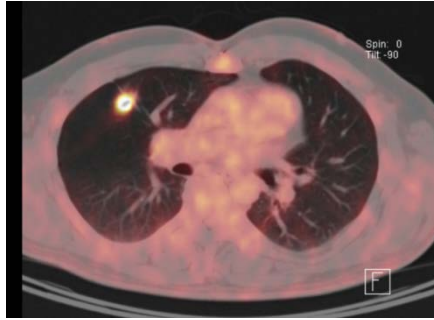
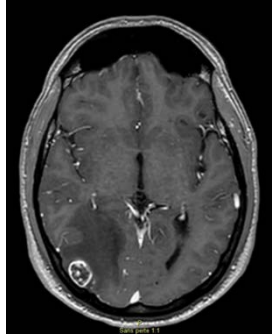


Quel LAT pour quels sites ?

Prise en charge de la maladie loco-régionale ?

Mr P. 52 ans
PS0
Aucun antécédent

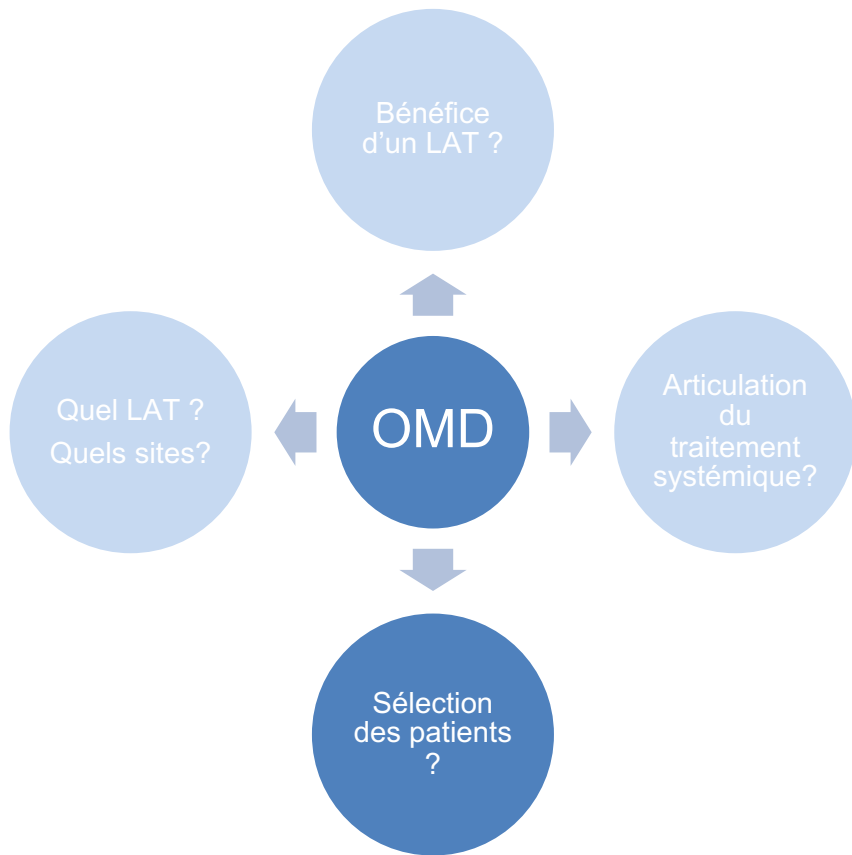
ADK PDL1 30%
T1c N1 M1b



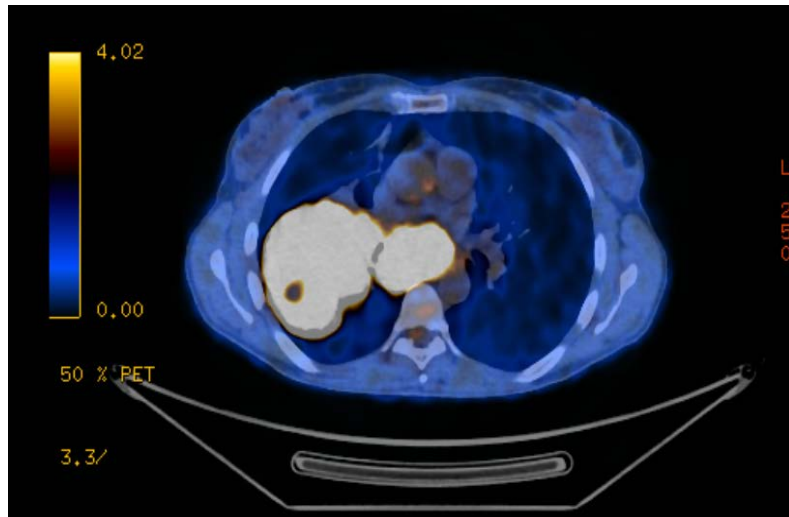
Mêmes règles de prise en charge que les patients M- ?
Ou devons-nous être « moins agressifs » ?



Problématiques de la gestion des OMD



Sélection des patients



Sélection des patients

	Multivariable Hazard Ratio (95% CI)	P
Synchronous Versus Metachronous		<.001
Synchronous	3.02 (1.74-5.26)	
Metachronous	1 Reference	
N Stage		.002 ^a
N0	1 Reference	
N1	1.69 (1.00-2.85)	.051
N2	1.93 (1.25-2.97)	.003
N3	8.28 (1.82-37.68)	.006
Histology		.001 ^a
Adenocarcinoma	1 Reference	
Large cell	2.39 (1.26-4.51)	.007
Squamous	1.86 (1.16-2.98)	.01
Other	6.26 (1.38-28.38)	.017

Données issues de 757 patients oligo-NSCLC :

- 1 à 5 métastases
- Synchrones ou métachrones
- Traitement direct : chir / SABR
- Traitement local du primitif

(Pas de données sur utilisation PET / MRI !)

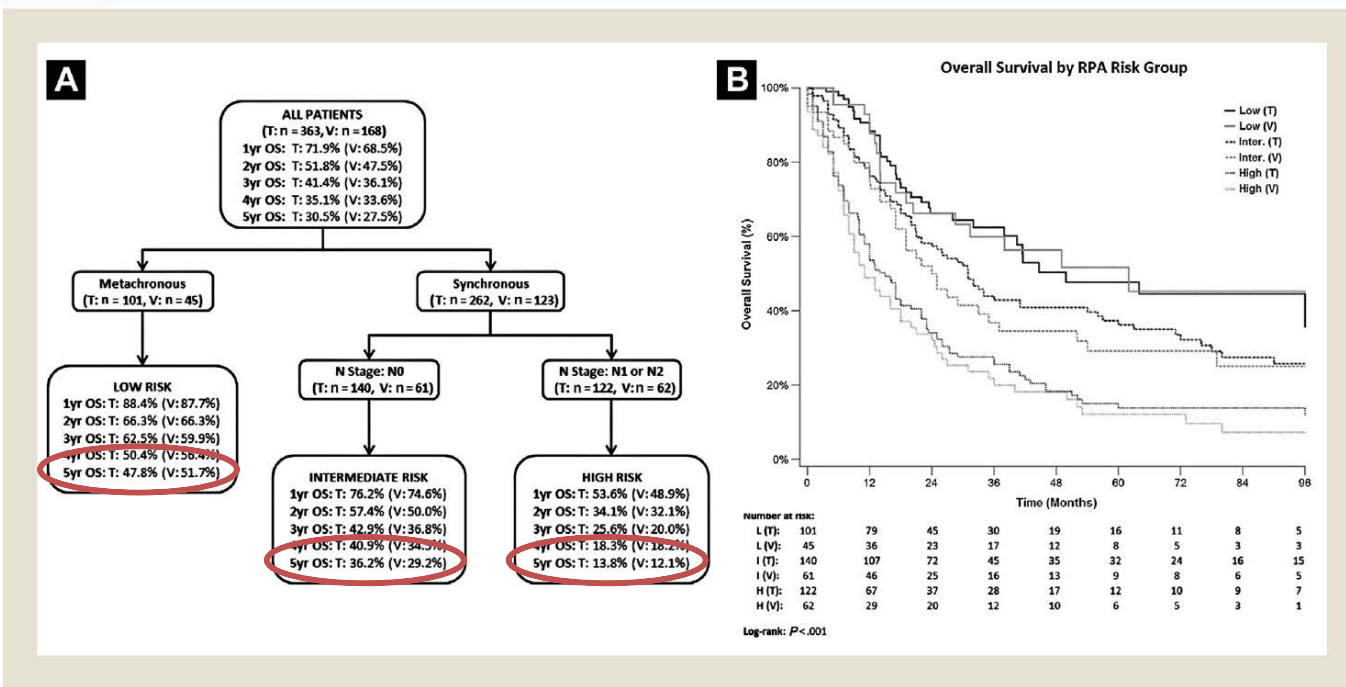
Pas d'impact sur l'OS de :

- Stade intra-thoracique
- Type de traitement local (chirurgie ou non)
- M+ cérébrale ou non
- M+ pulmonaire ou non

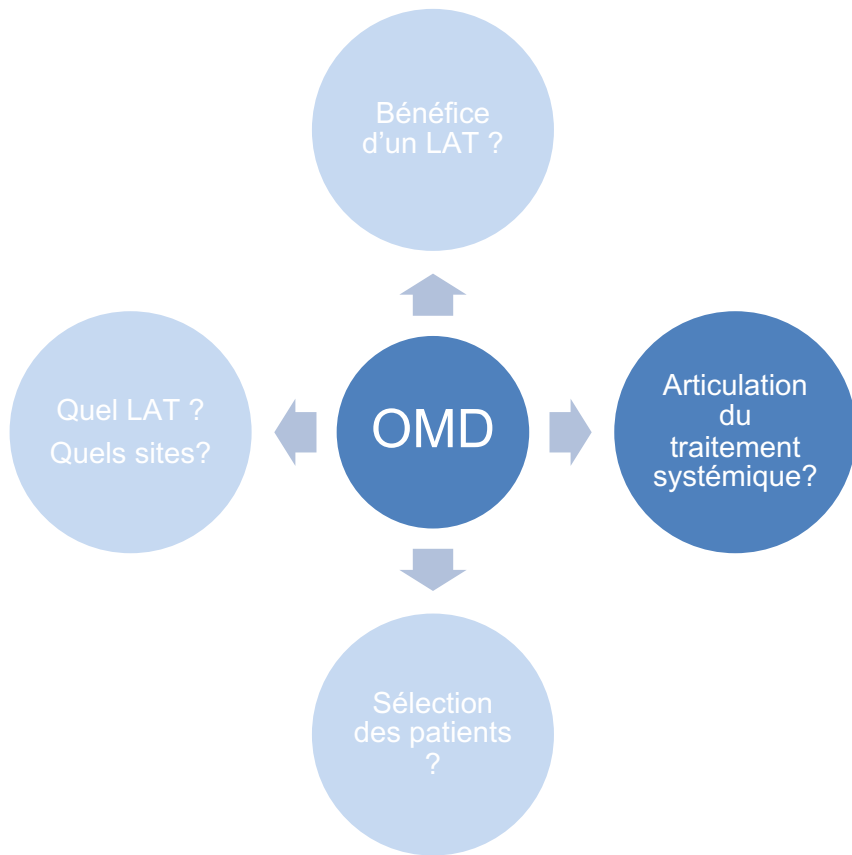


Sélection des patients

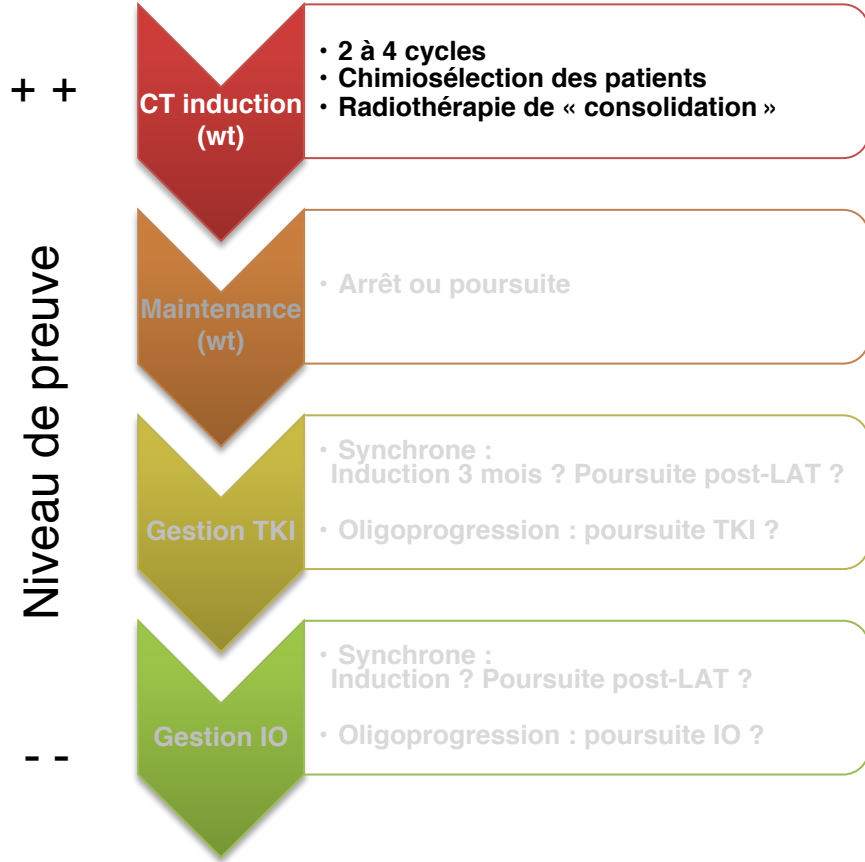
Figure 2 (A) Recursive Partitioning Analysis of OS in Oligometastatic NSCLC for the Training Set (T) n = 505, and Validating Set (V) n = 252, With (B) Corresponding Kaplan-Meier Estimates According to RPA Risk Group



Problématiques de la gestion des OMD



Articulation du Tx systémique ?



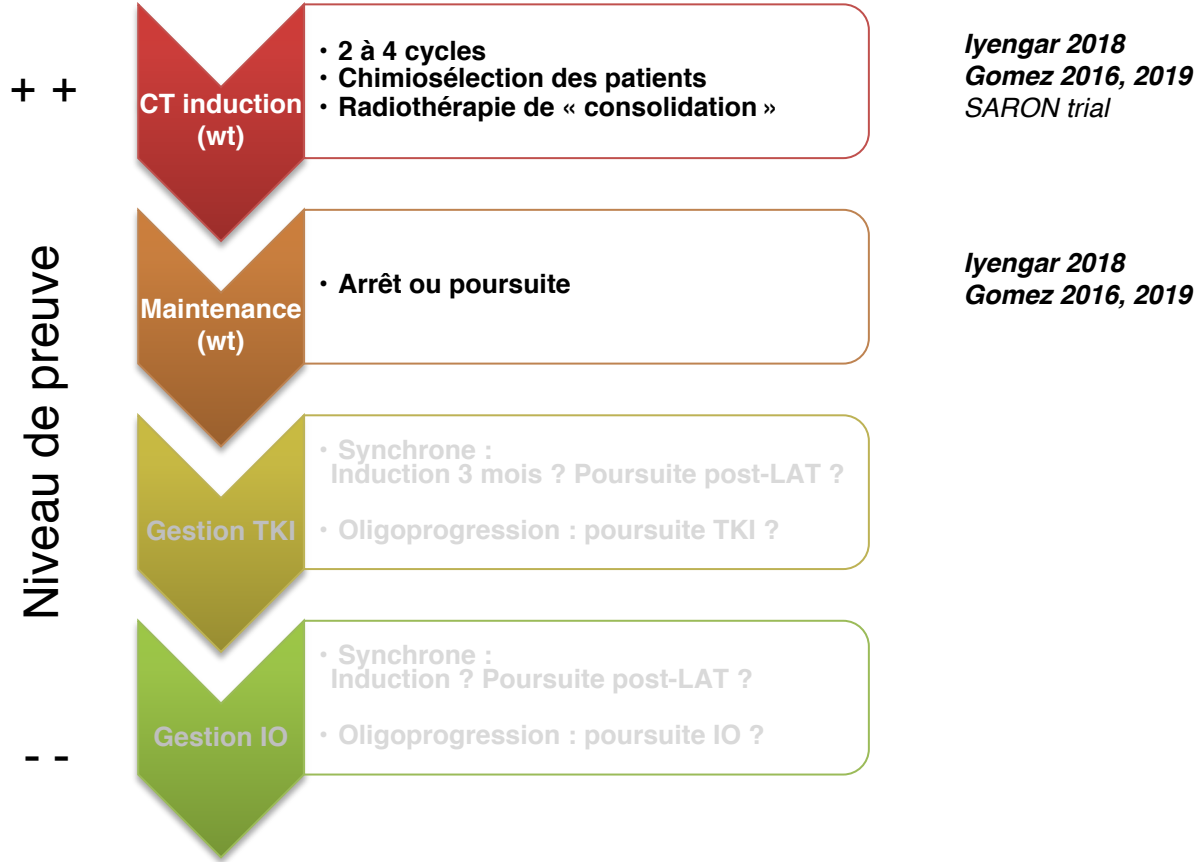
Iyengar 2018

Gomez 2016, 2019

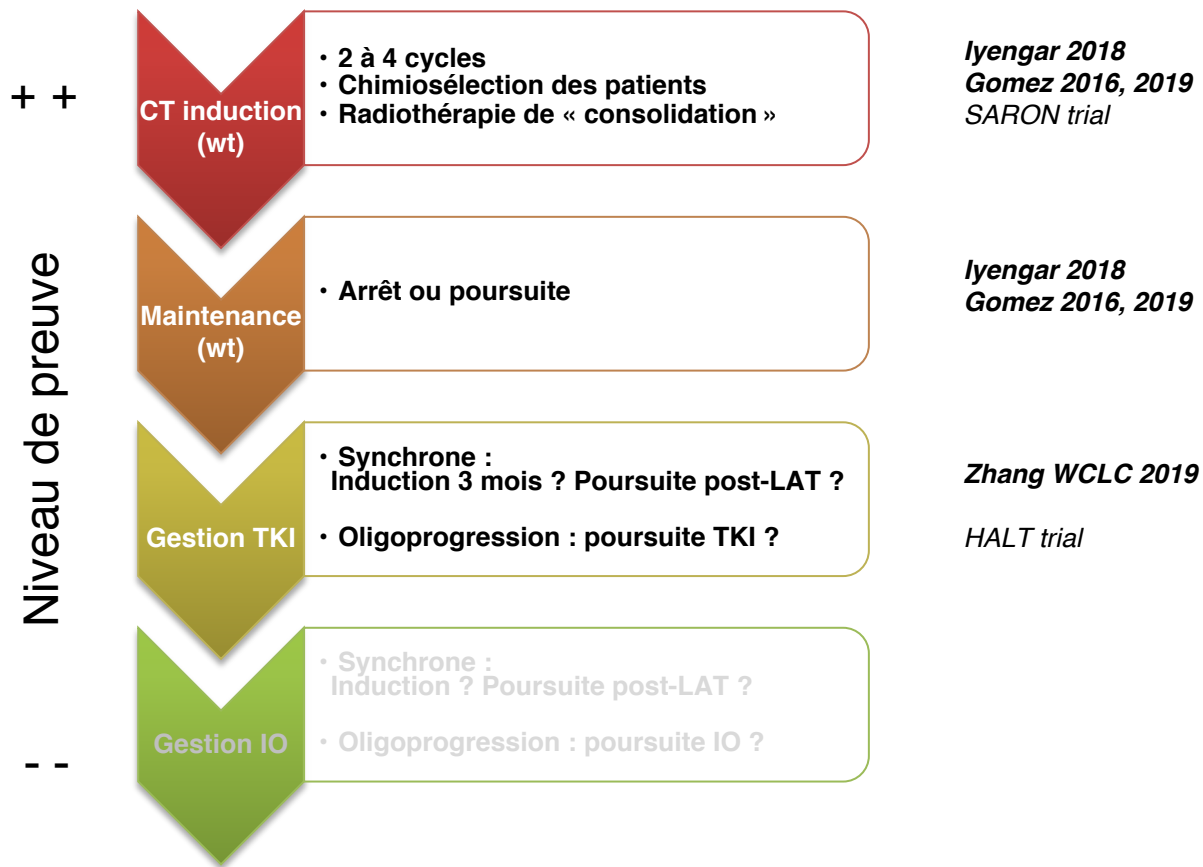
SARON trial



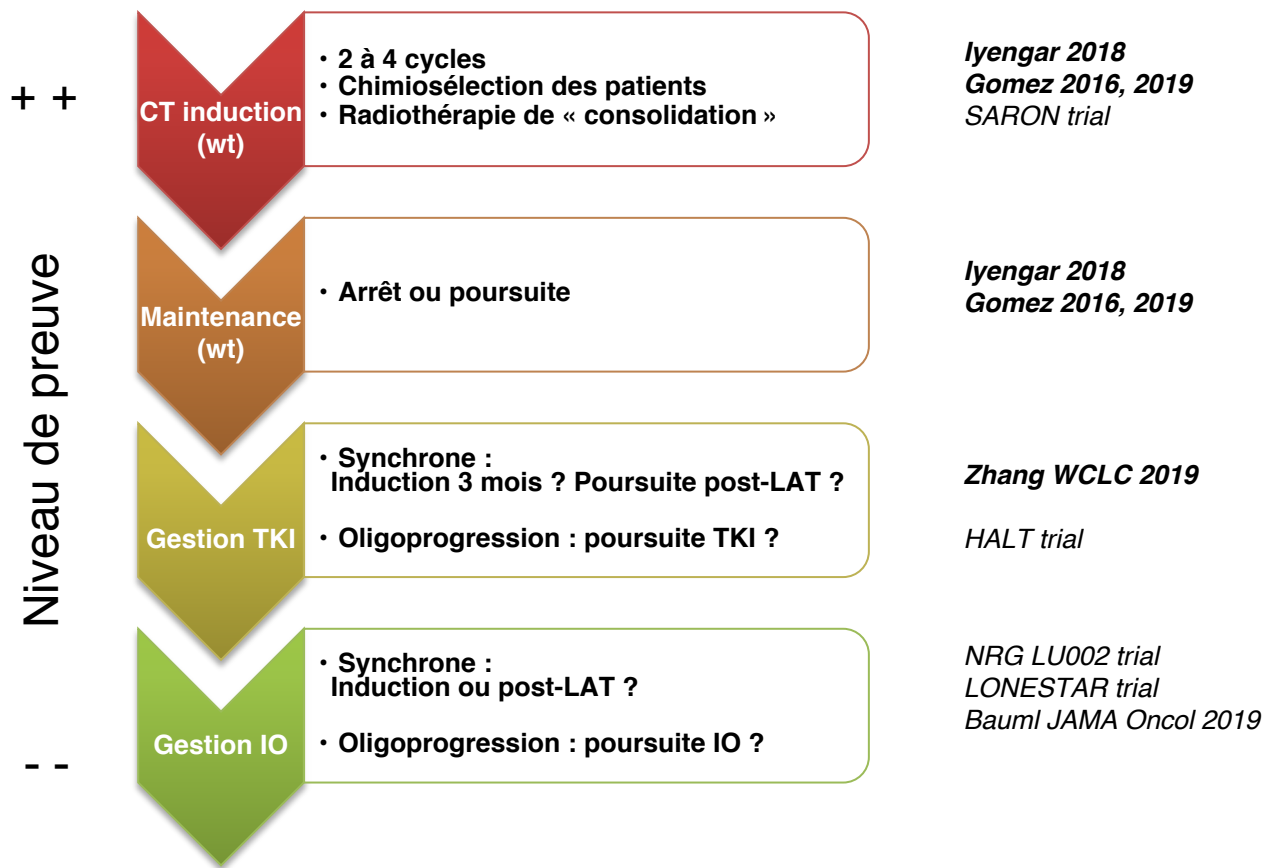
Articulation du Tx systémique ?



Articulation du Tx systémique ?

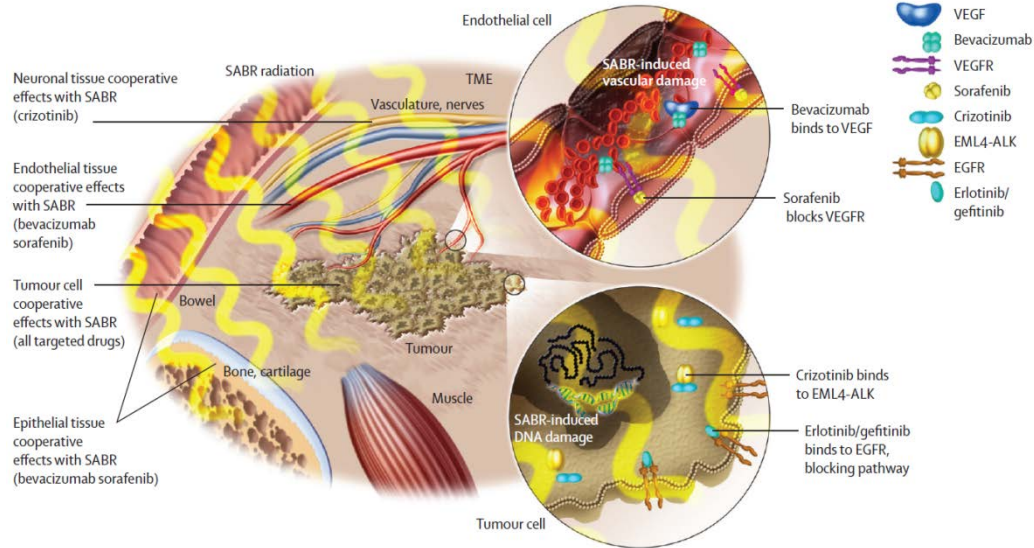


Articulation du Tx systémique ?

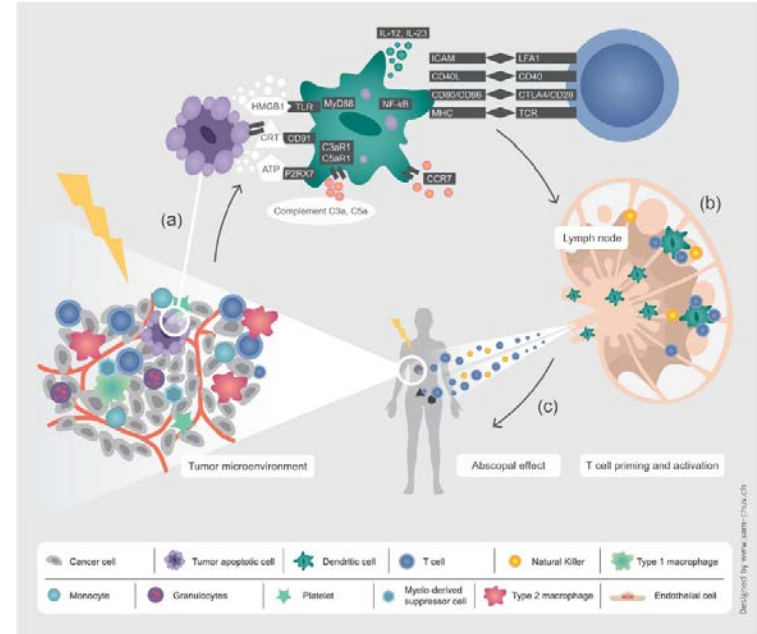


Articulation du Tx systémique ?

SBRT + thérapie ciblée

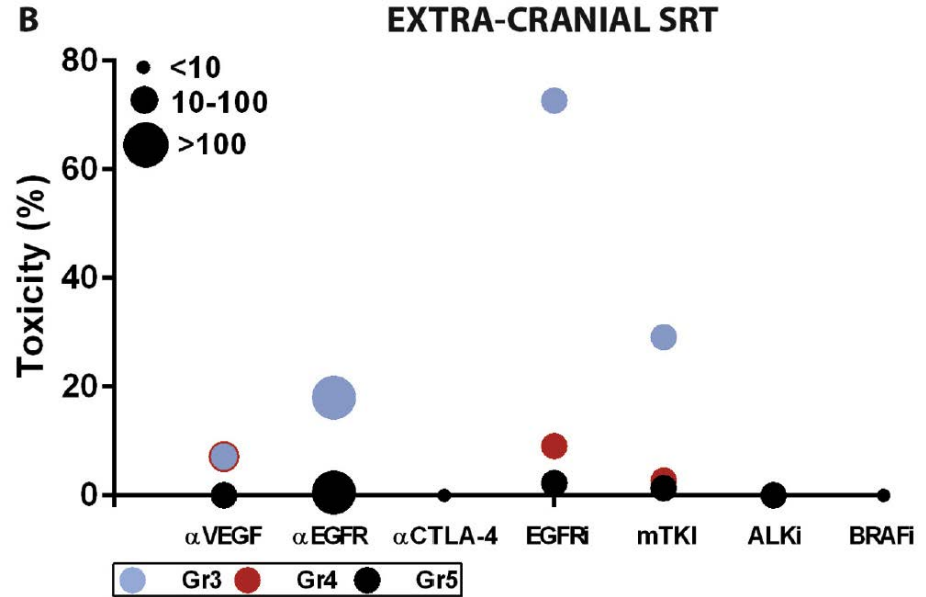
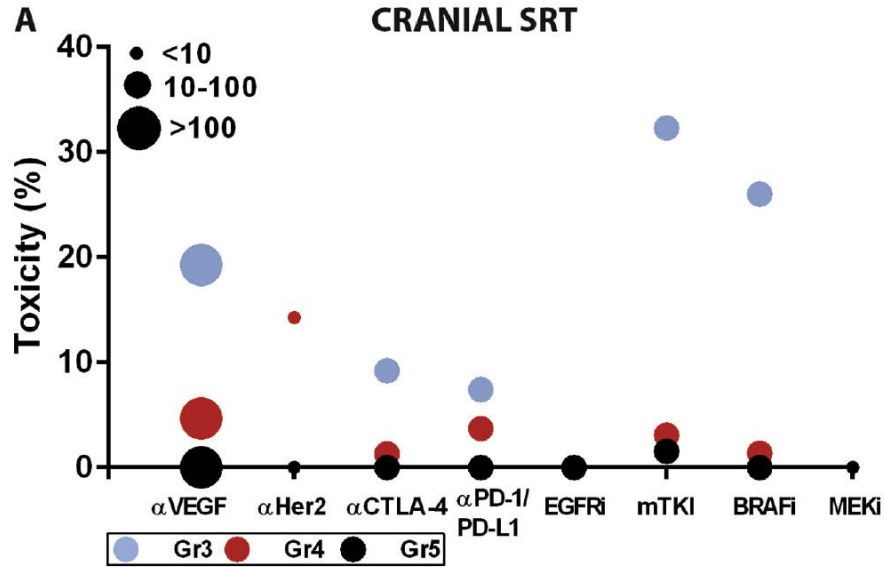


SBRT + immunothérapie



Articulation du Tx systémique ?

Toxicité de l'association ?



Conclusion

- « Etat oligométastatique »
 - Nouveaux concepts
 - Nouvelle « gestion du temps » (cf cancer du rein)
- Résultats prometteurs...à confirmer en phase III
- Possibilité d'extrapoler à d'autres histologies ?
- Nombreuses questions persistent
- Attention aux dérives... : privilégier les inclusions dans les essais !



COURS DU GOLF

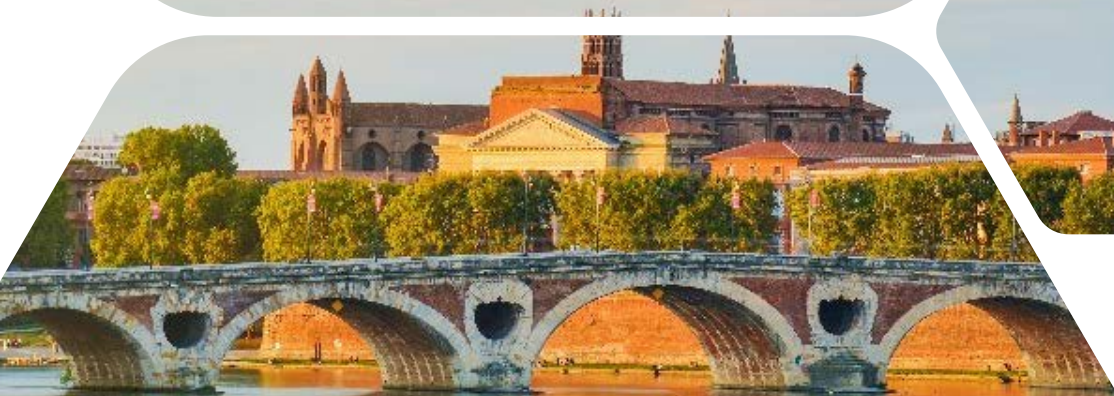
7 AU 10 OCTOBRE 2019

Groupe d'Oncologie de la Société de
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