LES MODIFICATIONS DU FRACTIONNEMENT

Vers un changement de paradigme

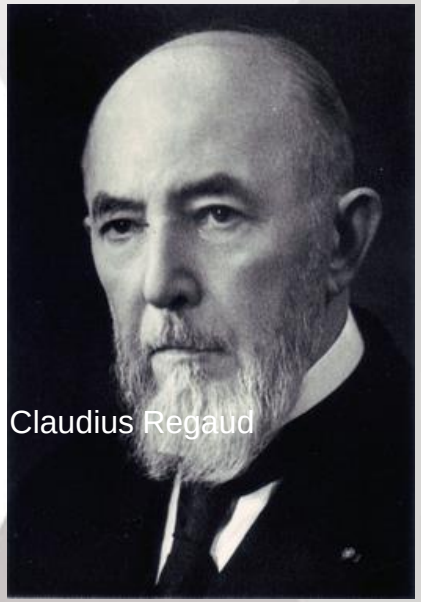
Cyrus CHARGARI

Septembre 2019

Le rationnel au fractionnement


Henri Coutard

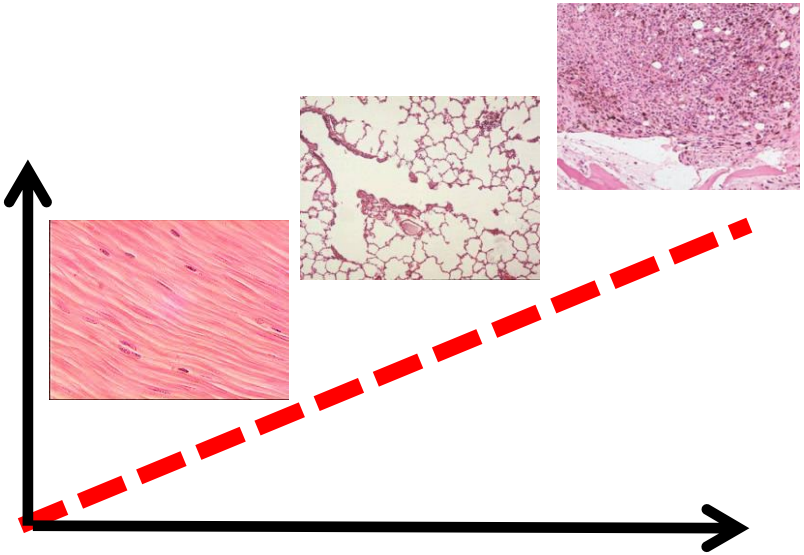
➔ **Traitement <u>étalé</u> et <u>fractionné</u>**


Claudius Regaud

Congrès International d'Oncologie, 1922

"des cancers du larynx peuvent être traités sans effet secondaire inacceptable

Facteurs de radiosensibilité



- **5 « Rs » de la RT:**
  - Réparation différentielle
  - Repopulation
  - Réarrangement
  - Radiosensibilité
  - Réoxygenation

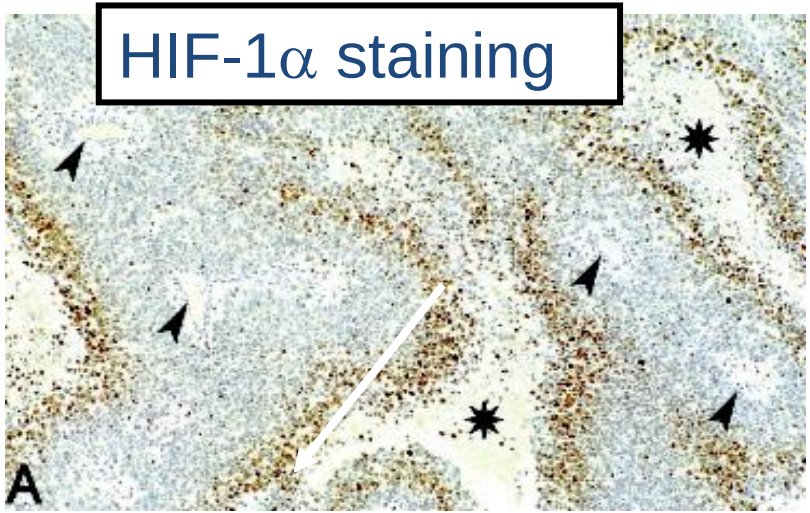
Cibles pharmacologiques

Post-mitotiques fixées — Intermitotiques

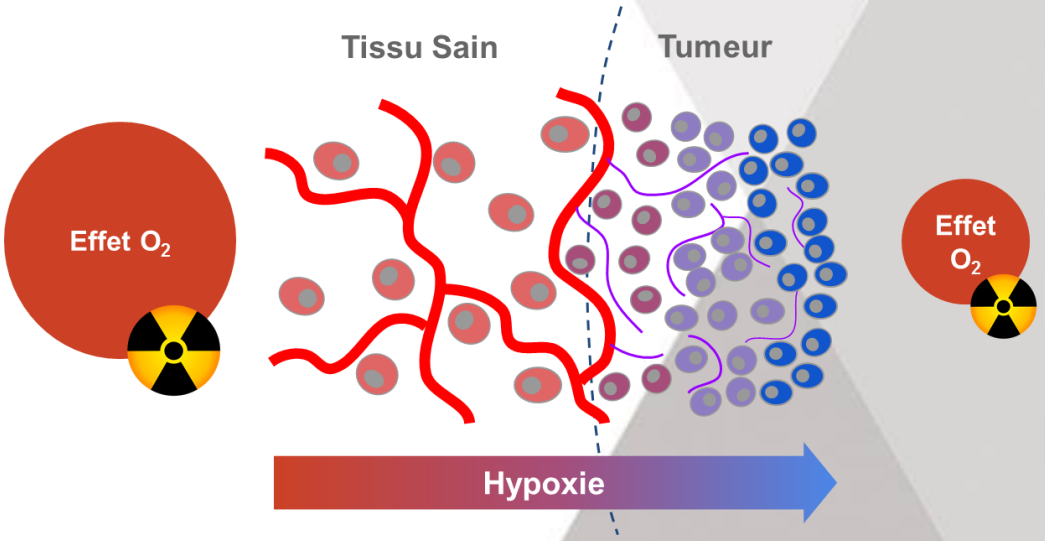
Différenciées ++ — Indifférenciées

Le rationnel au fractionnement

Effet oxygène

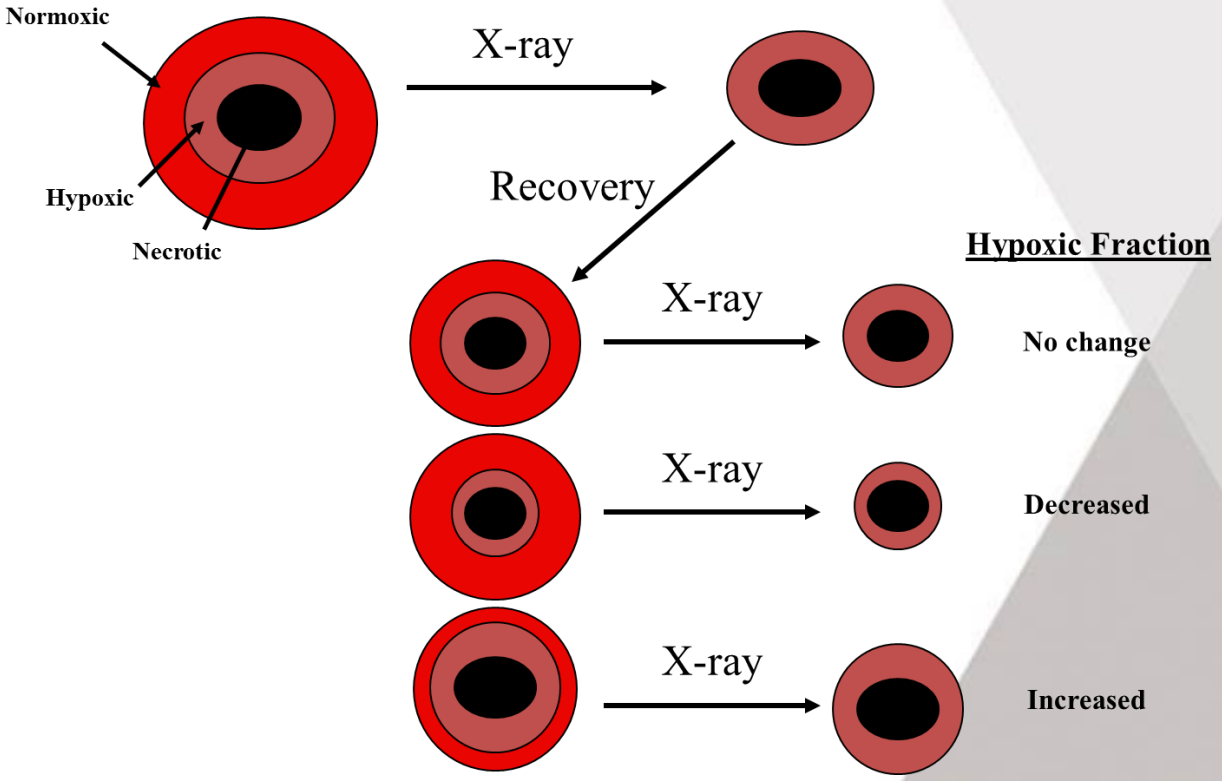


Blood vessels Necrosis

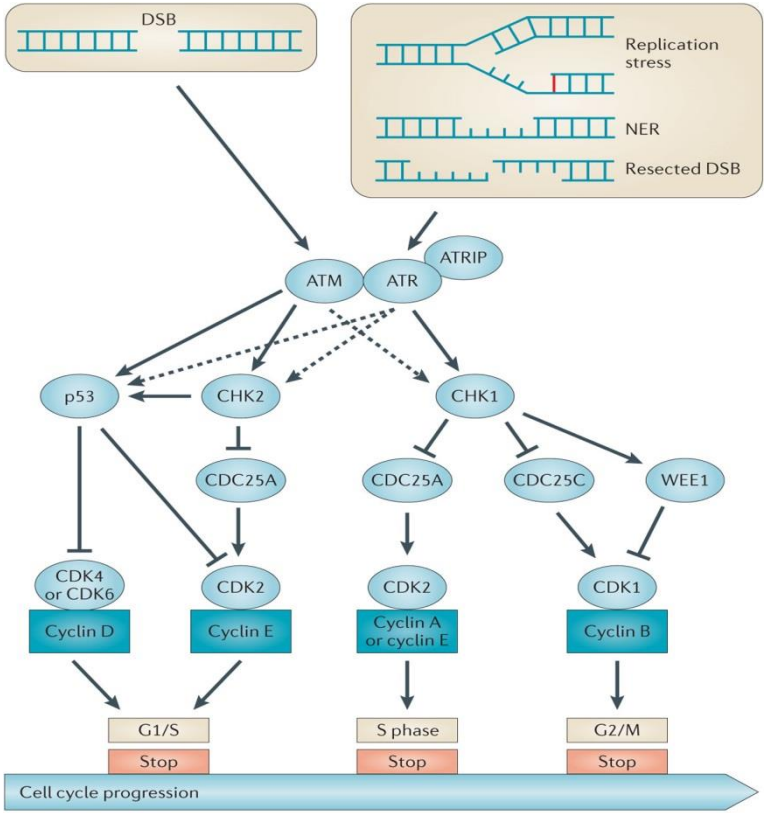


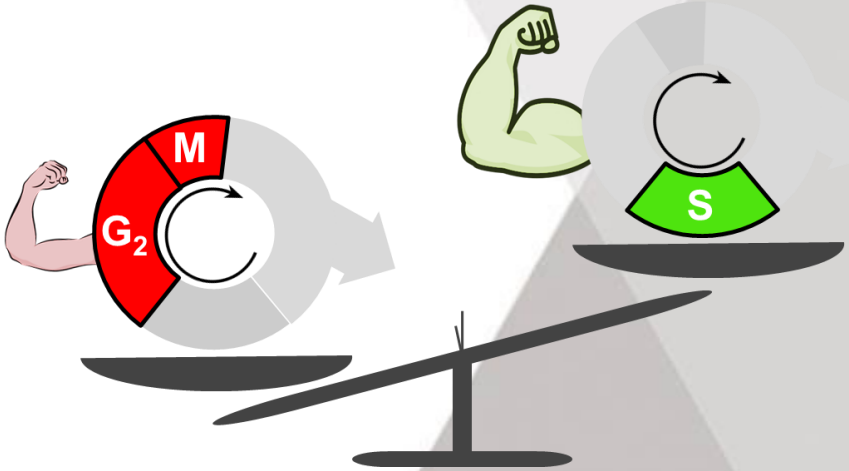
Le rationnel au fractionnement

Effet oxygène



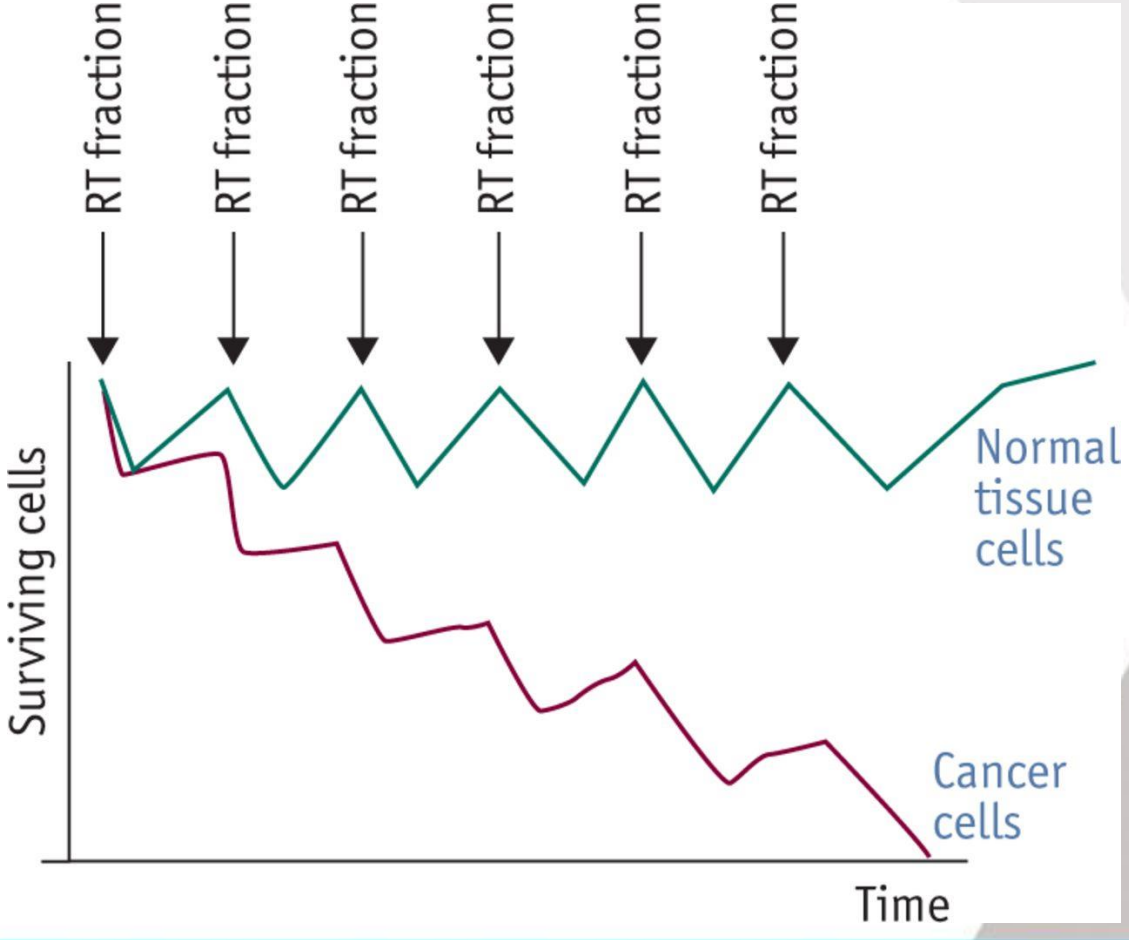
Le rationnel au fractionnement





Curtin et al. 2012

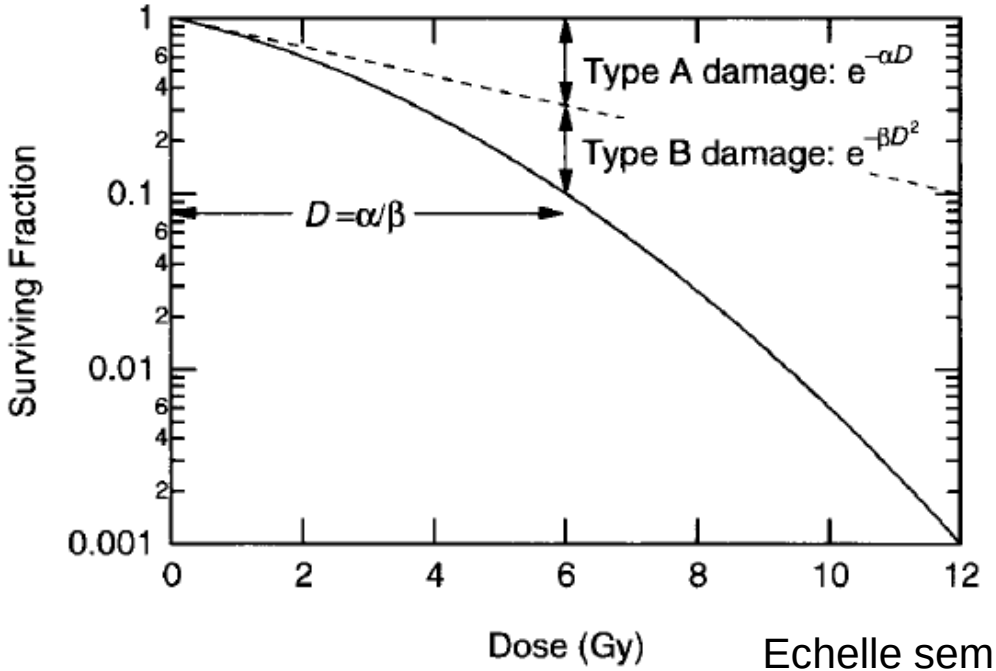
Pierre Annede



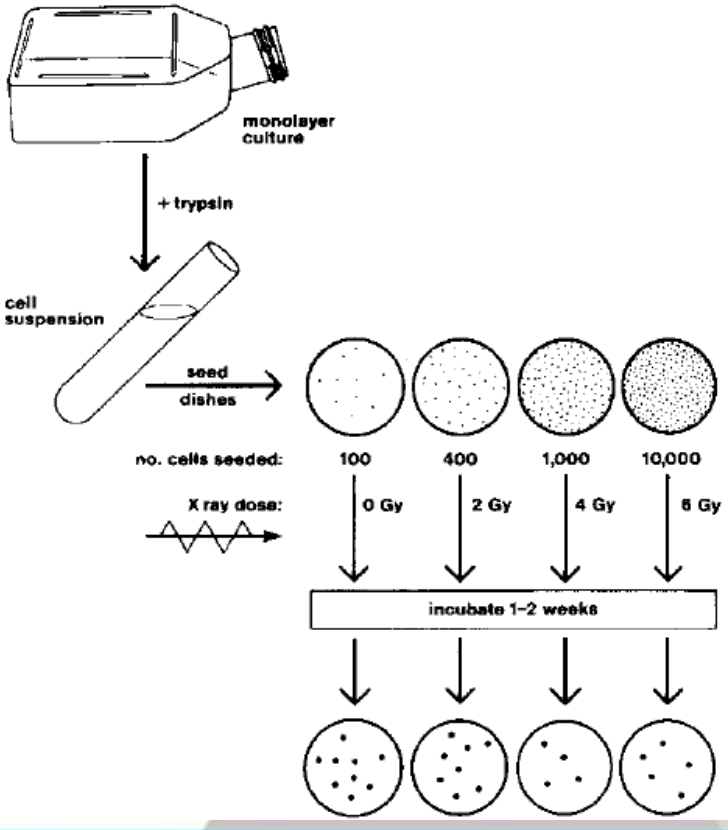
Putora et al. Breathe 2011

Fractionnement et effet différentiel

Modèle linéaire quadratique



Echelle semi-log



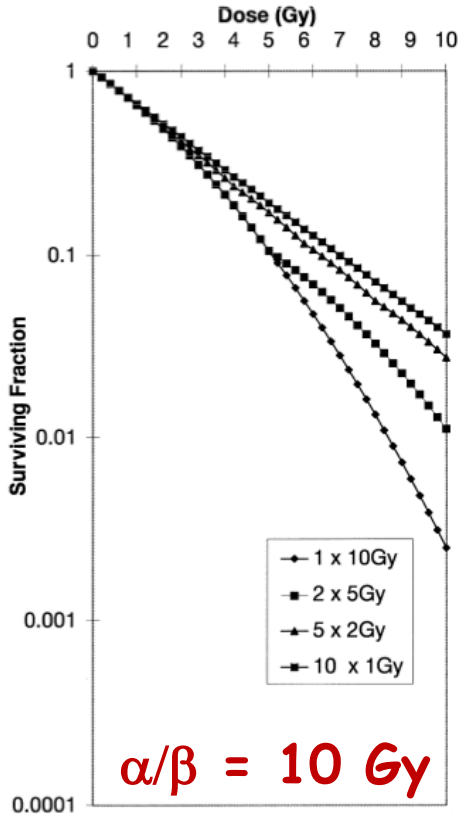
$$P_{\text{survival}} = e^{-\alpha D - \beta D^2}$$

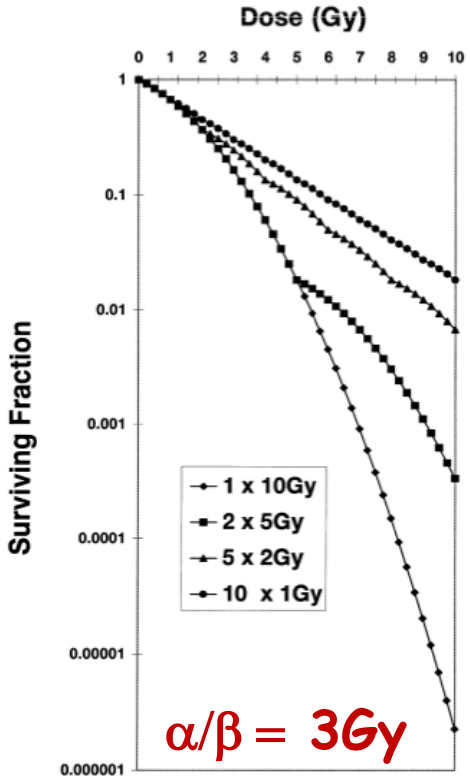
Fractionnement et effet différentiel

- **Sensibilité +++ des tissus à renouvellement lent ⇔ systèmes de réparation ➔ α/ β faible (2-5 Gy)**
  - Tissus non compartimentaux (SNC, tissus conjonctifs)
  - Responsables des effets tardifs +++
  - Certains cancers (prostate, mélanome)

- **Sensibilité (+/-) des tissus à renouvellement rapide (ex: tumeur) ➔ alpha/béta élevé (> 10 Gy)**
  - Tissus compartimentaux (hémato, épiderme, muqueuses)
  - Responsables des effets précoces ou aigus
  - Majorité des tumeurs (épithelioma)

Fractionnement et effet différentiel





$$D = D_0 (\alpha/\beta + d_0) / (\alpha/\beta + d)$$

Réparation complète des SLD
Absence de prolifération entre deux fractions

- **42 Gy en 6 fractions de 7 Gy**

α/β [Gy]	10

HDR	d [Gy]	BED [Gy]	EQD_2 [Gy]
D_1	7	**11,9**	9,9
D_2	7	**11,9**	9,9
D_3	7	**11,9**	9,9
D_4	7	**11,9**	9,9
D_5	7	**11,9**	9,9
D_6	7	**11,9**	9,9
TOTAL	**42 Gy**	**71,4**	**59,5**

α/β [Gy]	3

HDR	d [Gy]	BED [Gy]	EQD_2 [Gy]
D_1	7	23,3	**14,0**
D_2	7	23,3	**14,0**
D_3	7	23,3	**14,0**
D_4	7	23,3	**14,0**
D_5	7	23,3	**14,0**
D_6	7	23,3	**14,0**
TOTAL	**42 Gy**	**140**	**84**

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

The histopathologic evaluation of soft tissue changes in rabbit extremity after different dose-fractionation schemes of interstitial high dose rate (HDR) brachytherapy

REPORTS OF PRACTICAL ONCOLOGY AND RADIOTHERAPY 15 (2010) 165–171

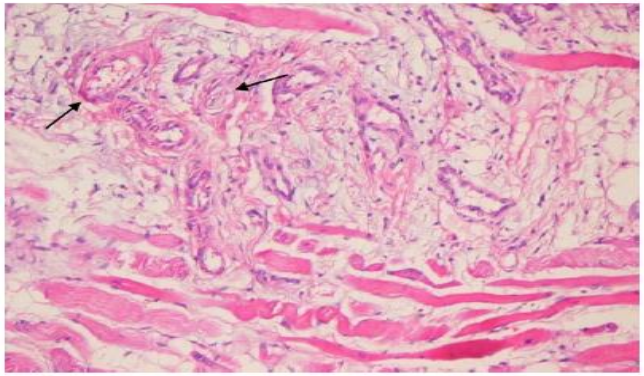


Fig. 1 – The irregular shape and diameter of vessels, HE×400.

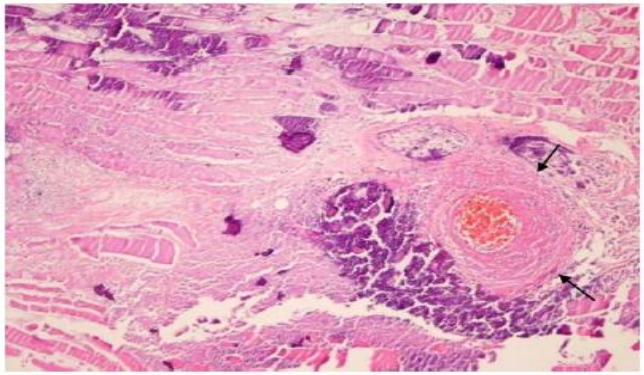


Fig. 2 – The fibrin accumulation, necrosis and calcification in vessel wall, HE×40.

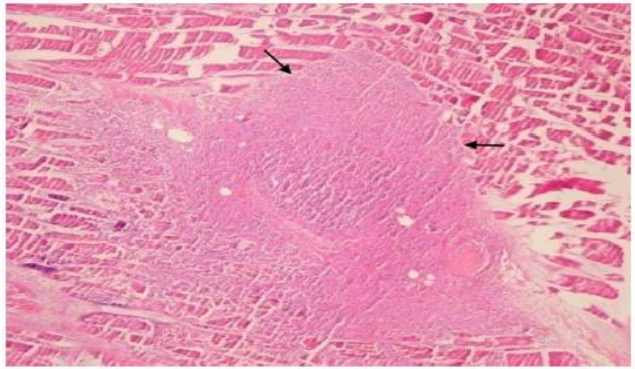


Fig. 3 – The necrosis in muscle tissue, HE×100.

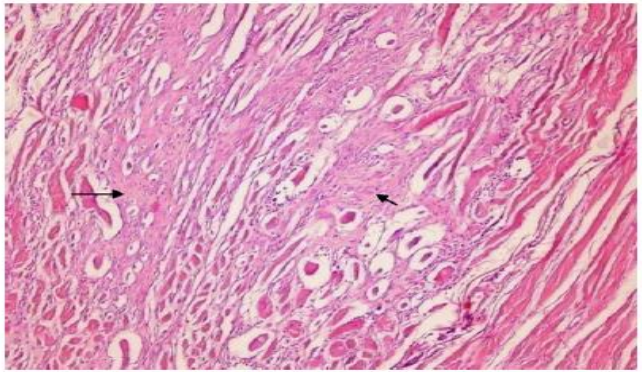


Fig. 4 – Atrophy and fibrosis of the muscle, HE×200.

Table 3 – The distribution of low and high grade of soft tissue pathologies among study groups.

	Study groups								
	A (n =10)	B (n =10)	p	A (n =10)	C (n =10)	p	B (n =10)	C (n =10)	p
STP-1									
Edema									
LG	8	4	0.085	8	2	0.012*	4	2	0.314
HG	2	6		2	8		6	8	
Inflammation									
LG	2	6	0.085	2	2	0.709	4	2	0.085
HG	8	4		8	8		6	8	
Endothelial proliferation									
LG	10	6	0.043*	10	4	0.005*	6	4	0.371
HG	–	4		–	6		4	6	
Necrosis									
LG	9	7	0.291	9	2	0.003*	7	2	0.035*
HG	1	3		1	8		3	8	
STP-2									
Muscle atrophy and deformation									
LG	9	4	0.029*	9	–	0.000*	4	–	0.043*
HG	1	6		1	10		6	10	
Calcification									
LG	6	4	0.328	6	2	0.085	4	2	0.314
HG	4	6		4	8		6	8	
Vascular hyalinization									
LG	10	10	–	10	6	0.043*	10	6	0.043*
HG	–	–		–	4		–	4	
Fibrosis									
LG	7	7	0.686	7	2	0.035*	7	2	0.035*
HG	3	3		3	8		3	8	

Ctrl

4x6Gy

13,5Gy

STP: soft tissue pathologies; group A: control arm; group B: fractionated HDR arm; group C: single fractionated HDR arm; LG: low grade; HG: high grade.

* $p \leq 0.05$, as statistically significant.

Fractionnement et effet différentiel

Cancer du col utérin

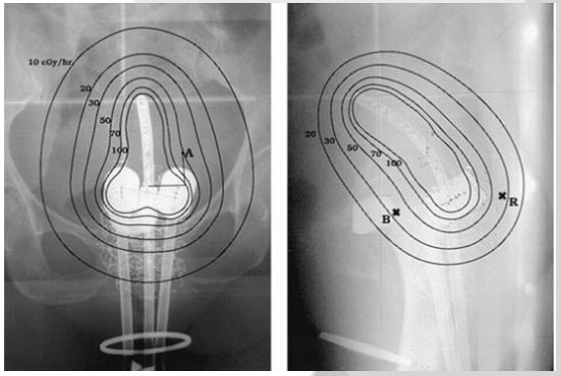
3 méta-analyses

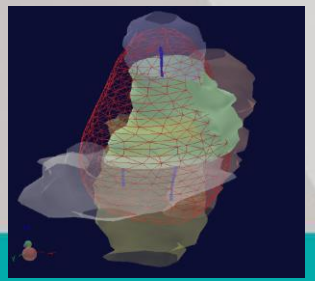
Pas de différence

BDD

Vs

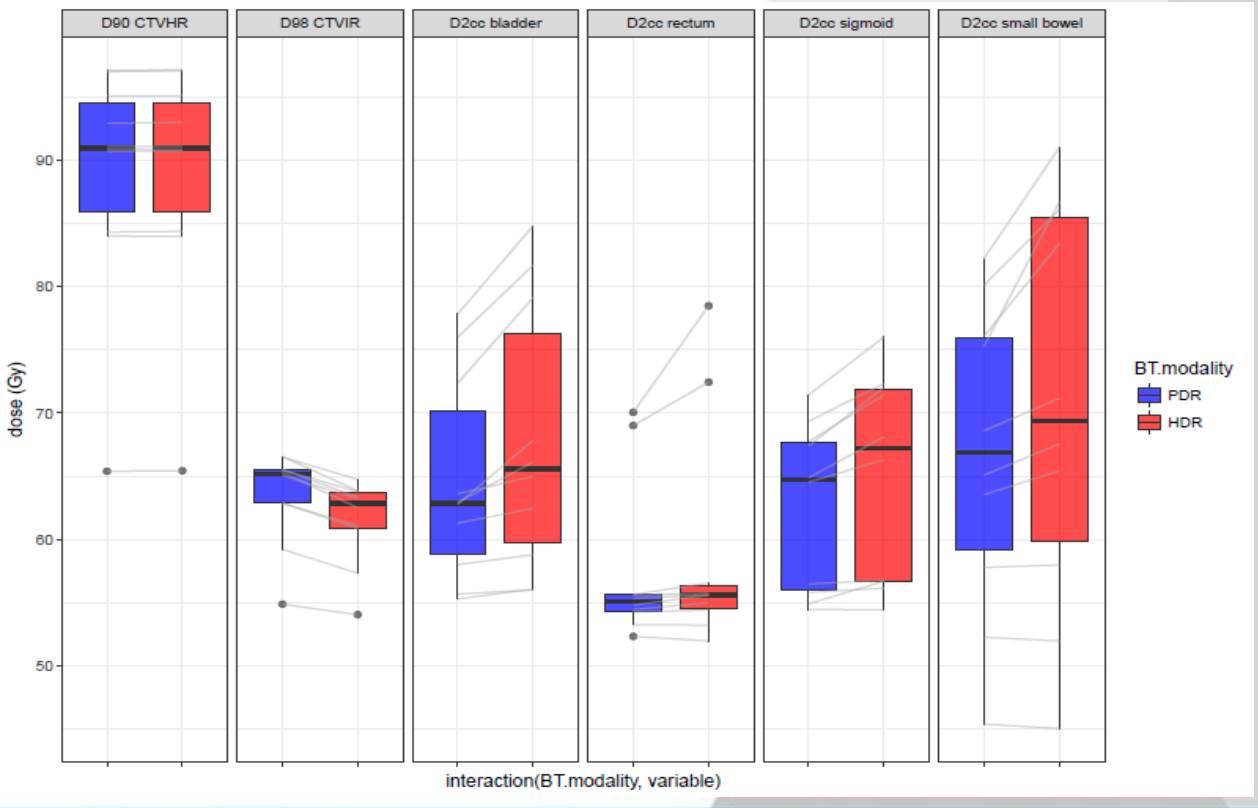
HDD



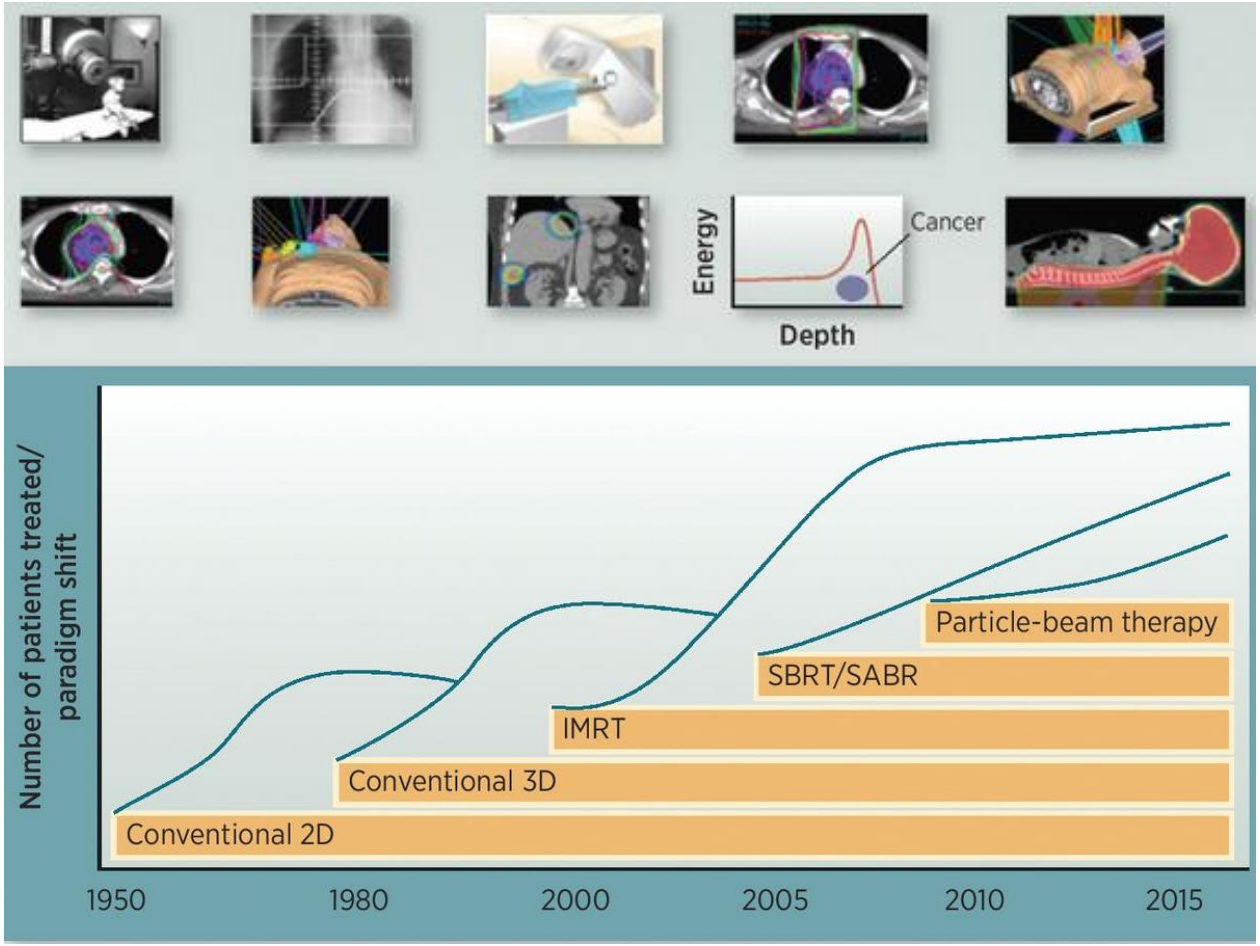


Fractionnement et effet différentiel

L'augmentation de la dose par fraction est un contre-sens biologique



Annede et al. Brachytherapy 2018



Remise en question par:

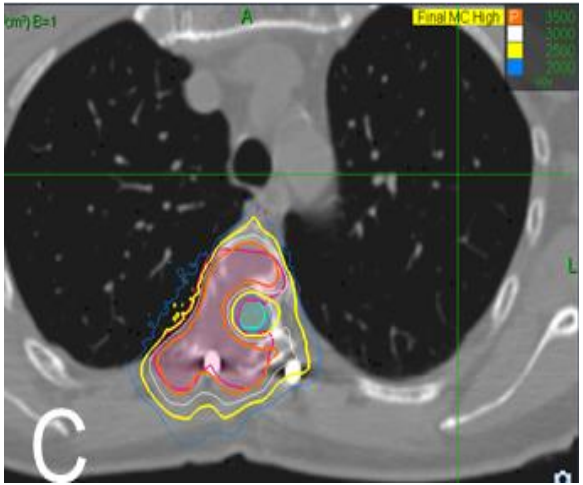
- Conformation accrue
- Repositionnement
- Systèmes de tracking
- Faisceaux MV, protons
- Curiethérapie

Quynh-Thu Le et al. CCR 2015

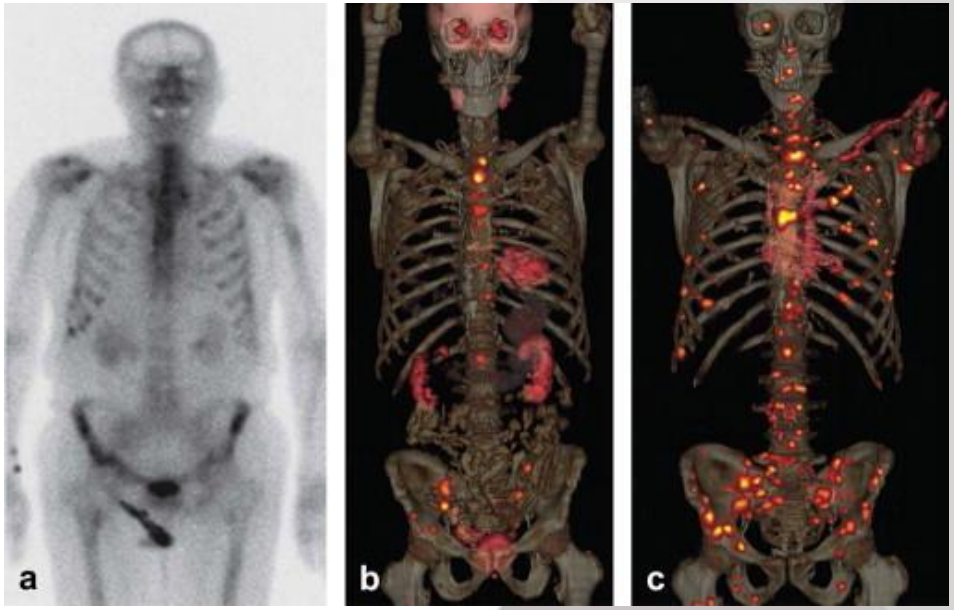
Nouveaux outils

RTS

- Escalade de dose
- Remise en question du 2-Gy/fr.
- RT part du traitement systémique



Concept oligo-métastatique



Sensibilité

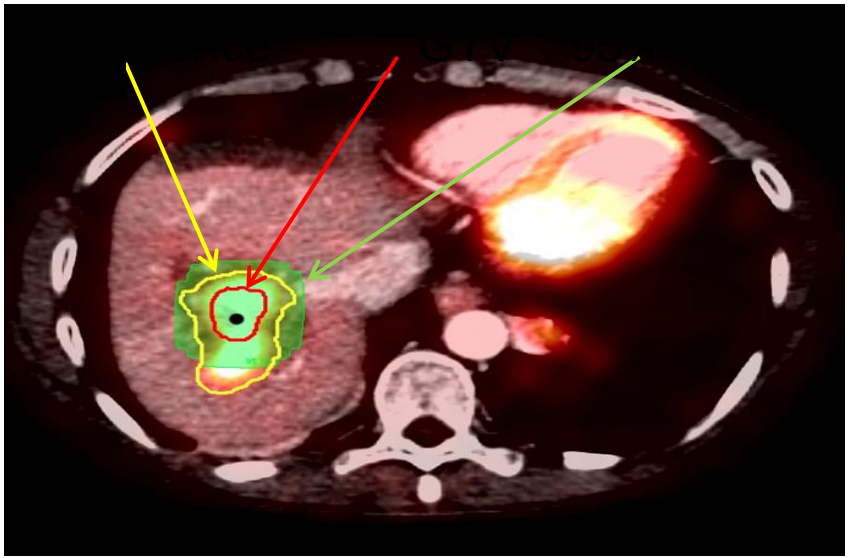
Chargari et al. Cancer Radiother 2017

Hricak et al. Radiology 2011

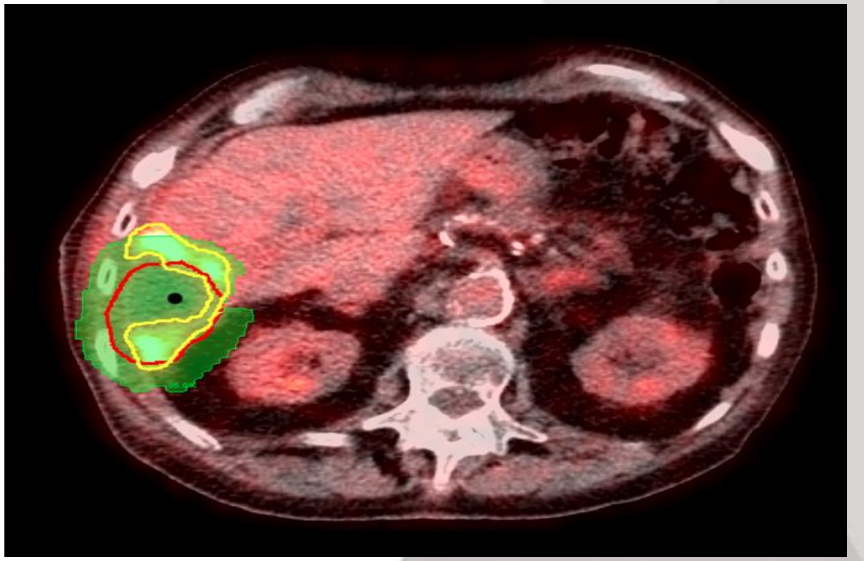
Nouveaux outils

Causes d'échecs

Rechute dans le GTV: dose



Rechute en bordure: volume



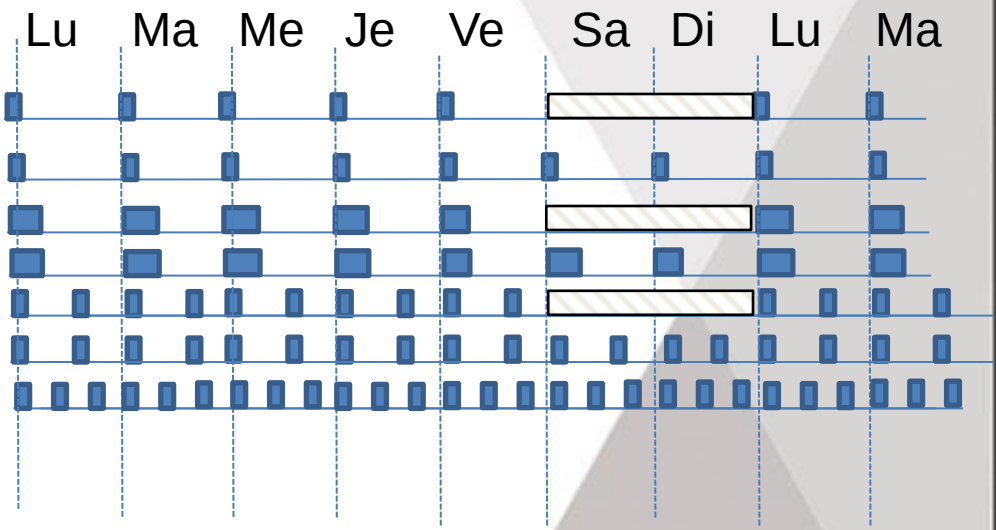
De Ridder, Radiother Oncol 2014

Modifications du fractionnement

Schedule	Total dose [Gy]	Dose/Fraction [Gy]	Fractions per day/per week
Conventional	60	2	1/5
Accelerated Conv.	60	2	1/7
Hypofractionated	60	4	1/5
Accelerated Hypo.	60	4	1/7
Hyperfractionated	60	1	2/10
Accelerated Hyper.	60	1	2/14
CHART	54	1.5	3/21
Split course	60	2	1/5
Concomittant boost	60	2	1–2/5–10

For better comparison of effects the integral dose for all runs has been chosen to be 60 Gy (except for CHART treatment with 54 Gy). In order to test the results of hypo- and hyperfractionation, extreme cases with doubled or halved doses per fraction where chosen. A visualisation of the according fractionation timings is presented in figure 4.

doi:10.1371/journal.pcbi.1003295.t002

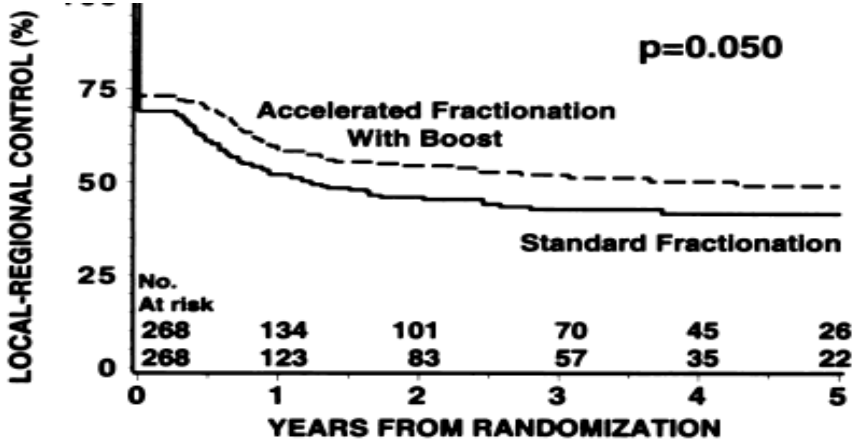


Kempf et al. PCBI 2013

Hyperfractionnement

- **Cancers ORL (RTOG 9003):**

1/ **Stdd**: 70 Gy 35 fr
2/ **Hyperfractionnée** 1,2 Gy/fr, 2/j, 5j/7 ➔ **81,6 Gy**/68 fr/7 sem
3/ **Accélérée** 1,6 Gy/fr, 2/j, 5j/7 ➔ 67,2 Gy en 42 fr/6 sem, dont 2 semaines de split
4/ **Accélérée boost conco** 1,8Gy/f, 5j/7, boost de 1,5 Gy/j les 12 derniers jours ➔ 72 Gy, 42 fr



Escalade de dose
Accélération

➔**Tox aiguë ++**

Aiguë

Table 3. Worst acute adverse effects of radiotherapy

		Standard fractionation (N = 268)	Hyper-fractionation (N = 263)	Accelerated fractionation with split (N = 274)	Accelerated fractionation with concomitant boost (N = 268)
	Grade	Number of patients (Percent)			
Maximum toxicity per patient	Grade1	12 (5)	9 (3)	20 (7)	11 (4)
	Grade2	154 (57)	102 (39)	113 (41)	95 (36)
	Grade3	94 (35)	142 (54)	133 (49)	155 (58)
	Grade4	0 (0)	2 (1)	5 (2)	2 (1)

Tardive

Table 5. Frequency of Grade 3 or worse late effects at various times after treatment start

Time after treatment start (months)	Standard fractionation	Hyper-fractionation	Accelerated fractionation with split	Accelerated fractionation with concomitant boost
	Number of patients/Number of patients at risk (Percent)			
6	26/248 (10)	35/247 (14)	22/254 (9)	32/249 (13)
12	21/191 (11)	25/187 (13)	15/198 (8)	20/196 (10)
18	7/145 (5)	20/160 (13)	14/146 (10)	9/150 (6)
24	7/111 (6)	17/135 (13)	9/116 (8)	10/128 (8)

➔**Pas d'augmentation de la toxicité tardive**

Hypofractionnement

- **Cancer du sein:**
  - 50 Gy en 25 fractions et 5 sem vs 42.5 Gy en 16 fractions et 22 jours
  - Ptes pN0, R0

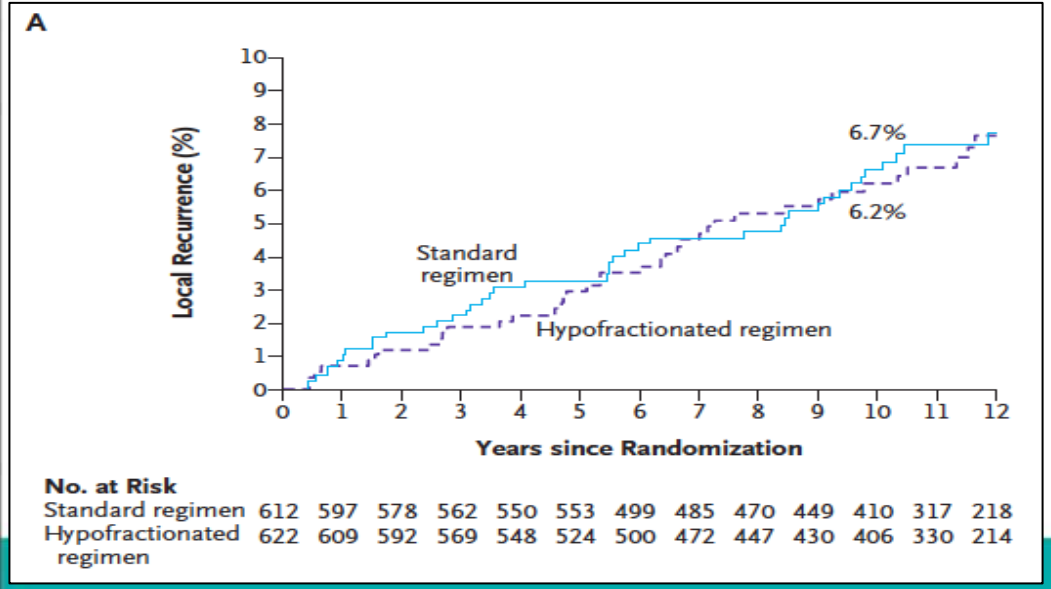
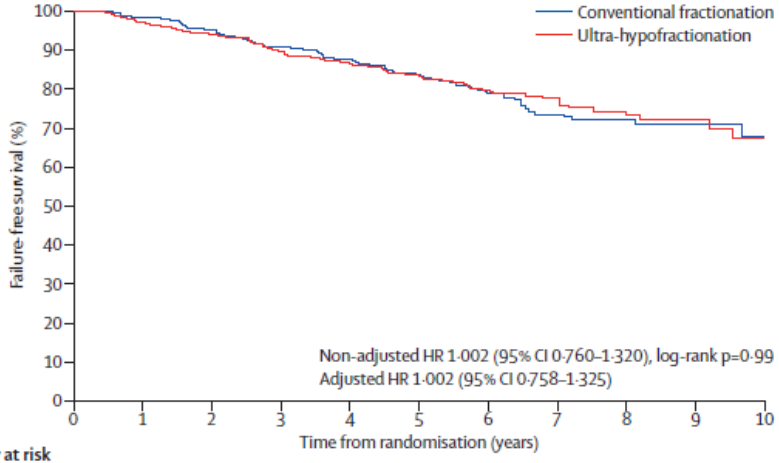


Table 2. Global Cosmetic Outcome, Assessed According to the EORTC Scale.*

Rating	5 Yr		
	Standard Regimen (N=423)	Hypofractionated Regimen (N=448)	Absolute Difference (95% CI)
	percent of patients		*percentage points*
Excellent	34.3	36.4	
Good	44.9	41.5	
Fair	17.3	19.0	
Poor	3.5	3.1	
Excellent or good	79.2	77.9	1.3 (−4.2 to 6.7)

Whelan et al. NEJM 2010

Hypofractionnement



Number at risk (number censored)											
Conventional fractionation	591 (0)	580 (4)	540 (24)	433 (108)	332 (196)	242 (273)	171 (332)	108 (386)	67 (425)	37 (454)	23 (467)
Ultra-hypofractionation	589 (0)	569 (4)	527 (27)	408 (125)	325 (196)	242 (269)	160 (342)	113 (385)	71 (423)	38 (454)	20 (470)

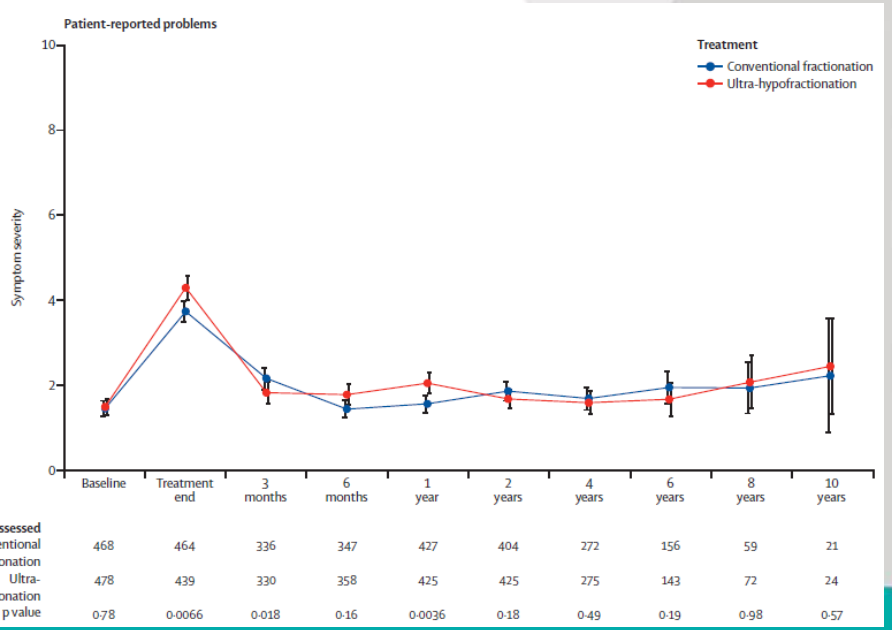
42,7 Gy en 7 fr, 3 j/semaine, 2,5 sem.
vs 78·0 Gy en 39 fr.

Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial

Anders Widmark, Adalsteinn Gunnlaugsson, Lars Beckman, Camilla Thellenberg-Karlsson, Morten Hoyer, Magnus Lagerlund, Jon Kindblom, Claes Ginman, Bengt Johansson, Kirsten Björnlinger, Mihajl Seke, Måns Agrup, Per Fransson, Björn Tavelin, David Norman, Björn Zackrisson, Harald Anderson, Elisabeth Kjellén, Lars Franzén, Per Nilsson

Lancet 2019; 394: 385–95

Pas pour objectif d'améliorer TCP/NTCP



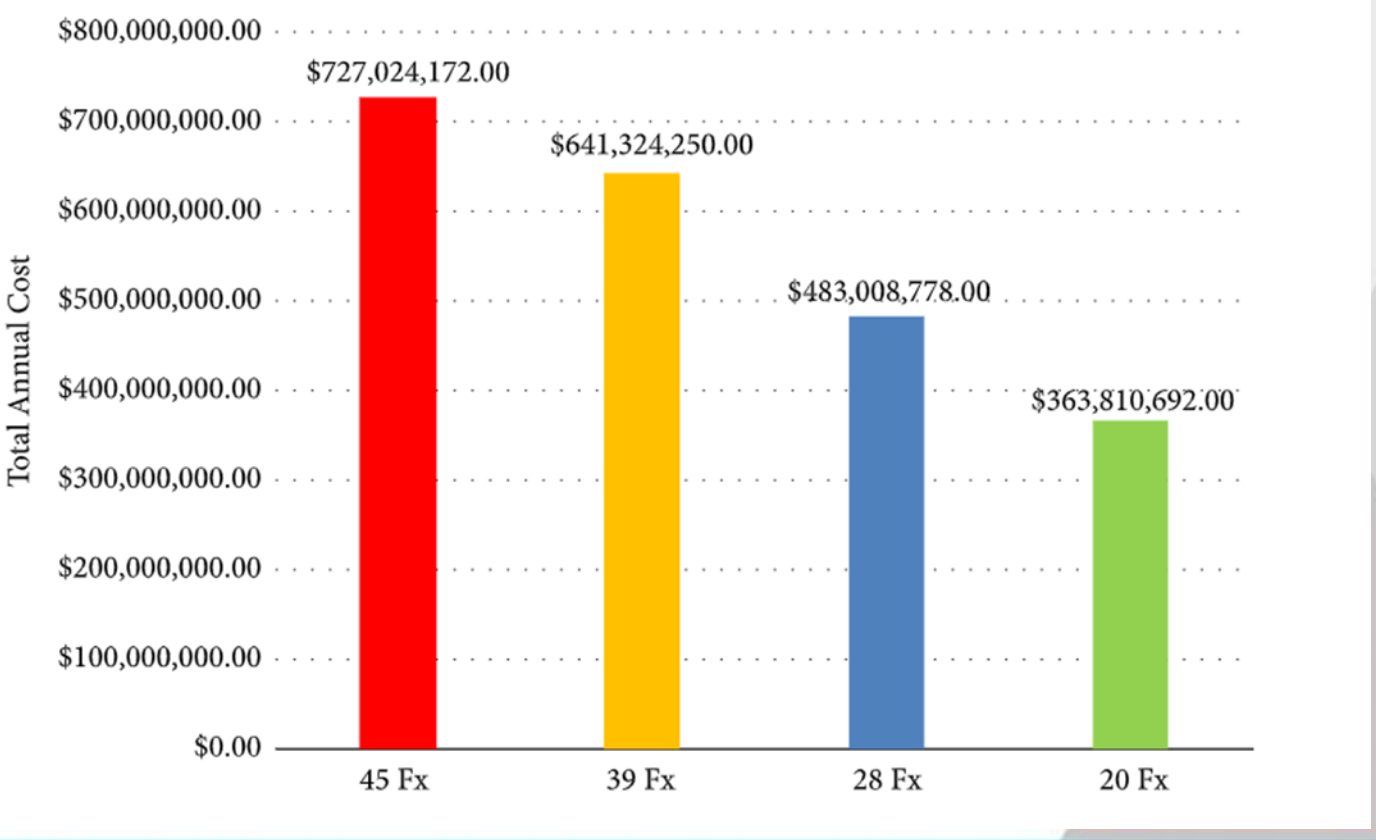
Number assessed										
Conventional fractionation	468	464	336	347	427	404	272	156	59	21
Ultra-hypofractionation	478	439	330	358	425	425	275	143	72	24
p value	0·78	0·0066	0·018	0·16	0·0036	0·18	0·49	0·19	0·98	0·57

Modifications du fractionnement

- **Quels sont les VRAIS objectifs de l'hypofractionnement?**
  - Améliorer le contrôle tumoral (α/β faible)? ➔ Si escalade de dose
  - Améliorer prédictivité de la dosimétrie
  - Médico-économique
    - Occupation des machines
    - Réduction des coûts
  - Nouveaux effets biologiques?
    - Microenvironnement
    - Immunomodulation

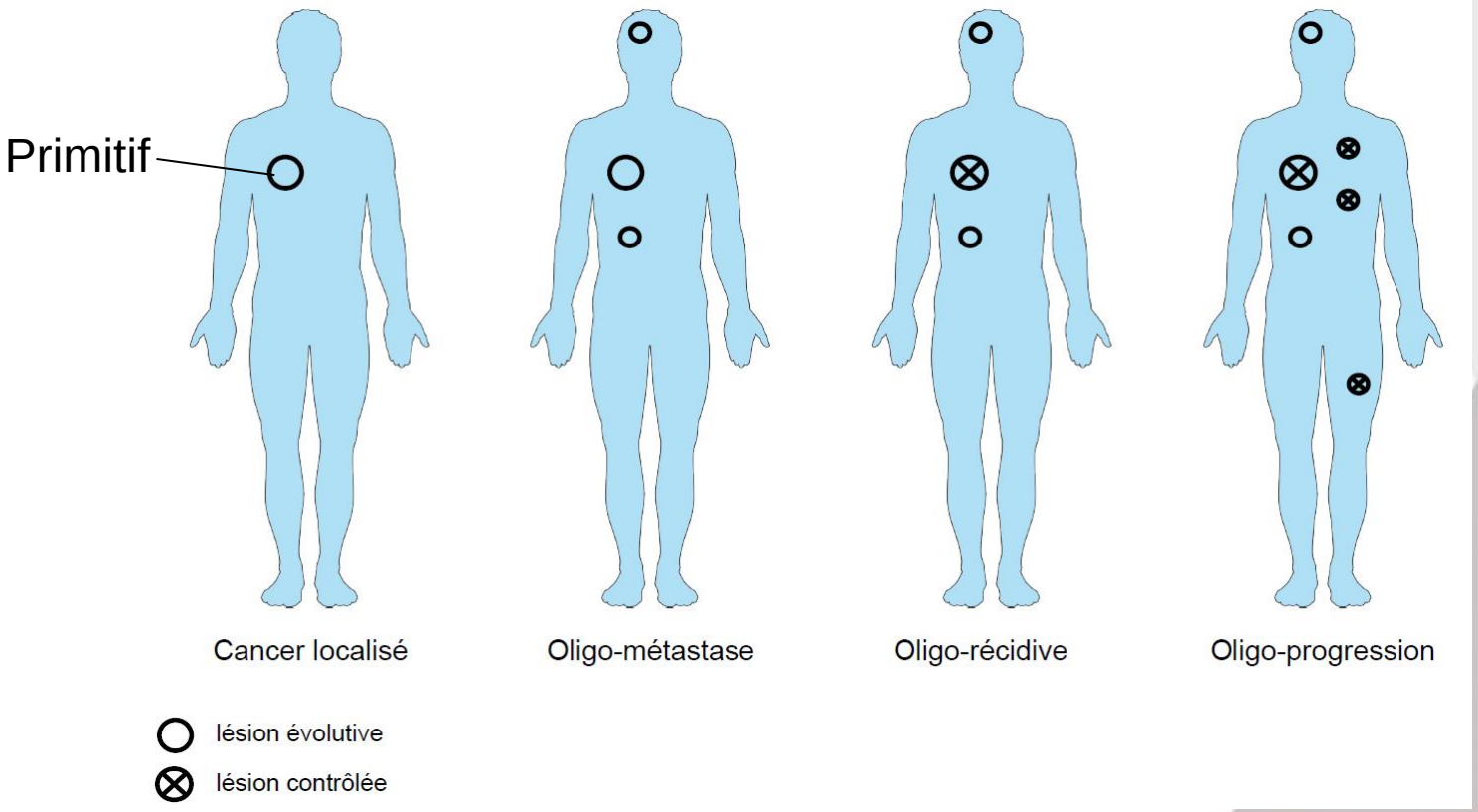
- **Amélioration de l'index thérapeutique ???**

Modifications du fractionnement



Moore et al. Journal of Oncology 2019

Maladie oligométastatique



Annede et al. Cancer Radiother 2019

Maladie oligométastatique

JAMA Oncology | Original Investigation

Consolidative Radiotherapy for Limited Metastatic Non-Small-Cell Lung Cancer

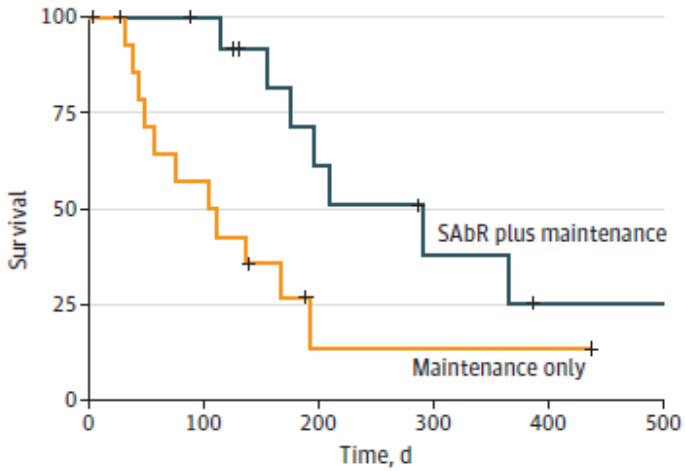
A Phase 2 Randomized Clinical Trial

≤ 5 métastases

Patients non progresseurs après induction

Traitement / SABRT

Figure 2. Analysis of Progression-Free Survival



No. at risk					
SAbR plus maintenance	14	12	6	3	1
Maintenance only	15	8	1	1	1

Log-rank testing reveals a statistically significant benefit in progression-free survival for SAbR-plus-maintenance chemotherapy (hazard ratio, 0.304; 95% CI, 0.113-0.815; *P* = .01). SAbR indicates stereotactic ablative radiotherapy.

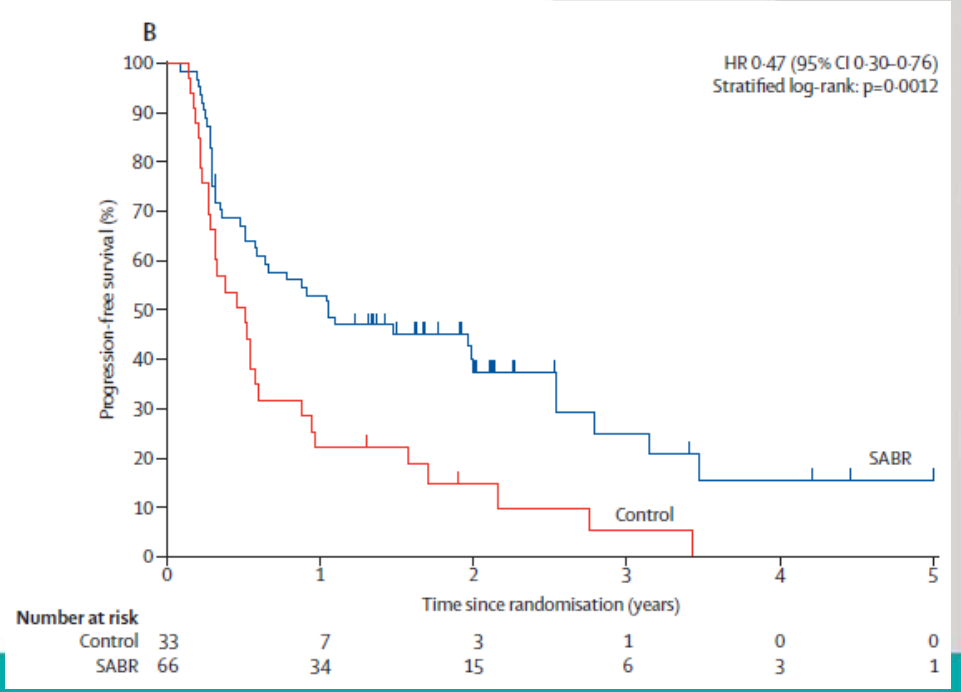
Maladie oligométastatique

T. Primitive contrôlée
1-5 métastases

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

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%)

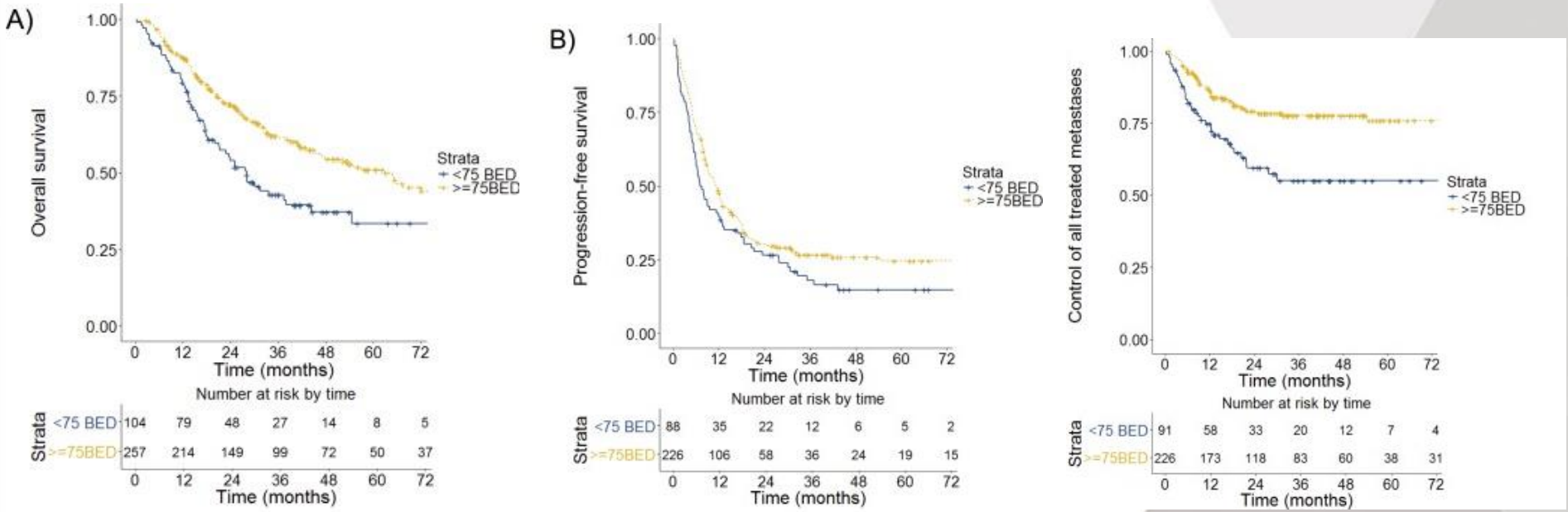
	All patients (n=99)	Control group (n=33)	Stereotactic ablative radiotherapy group (n=66)	p value
Adverse event grade ≥2	55 (56%)	15 (46%)	40 (61%)	0·15
Related adverse event grade ≥2	22 (22%)	3 (9%)	19 (29%)	0·026
Adverse event associated with death (grade 5)	3 (3%)	0	3 (5%)	0·55



Palma et al. Lancet 2019

Maladie oligométastatique

Oligométastases extra-craniales traitées par RT hypofractionnée guidée par imagerie

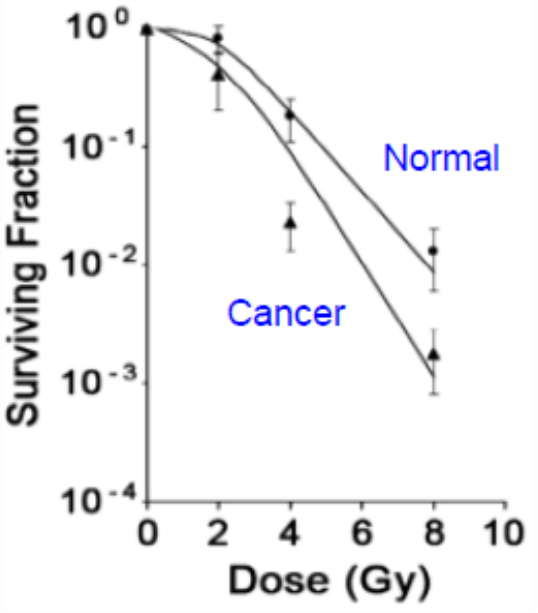


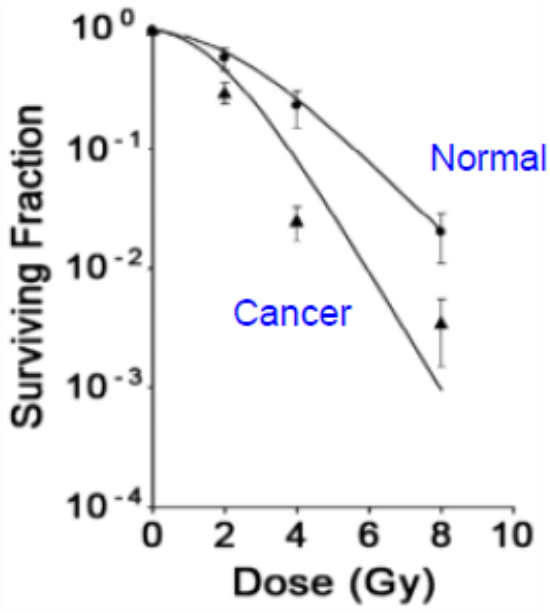
Hong et al. PlosOne 2018

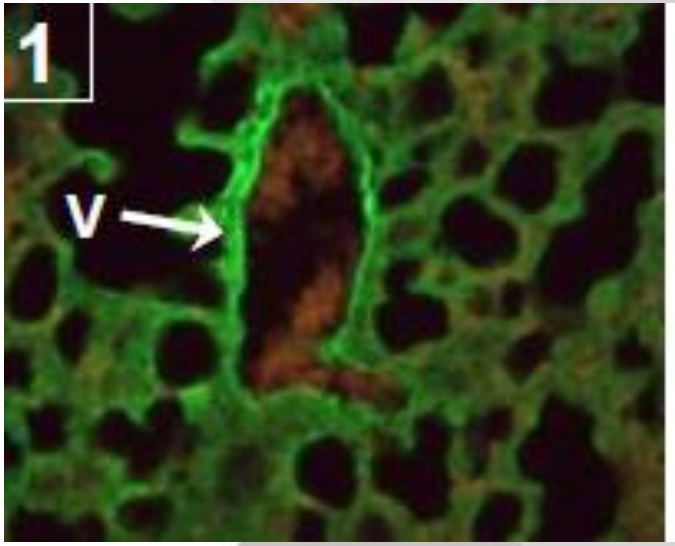
Nouveaux fractionnements ➔ Nouvelle biologie

HD / fractions ⇔ Effets vasculaires

Cellules endothéliales de tumeurs ou tissus sains





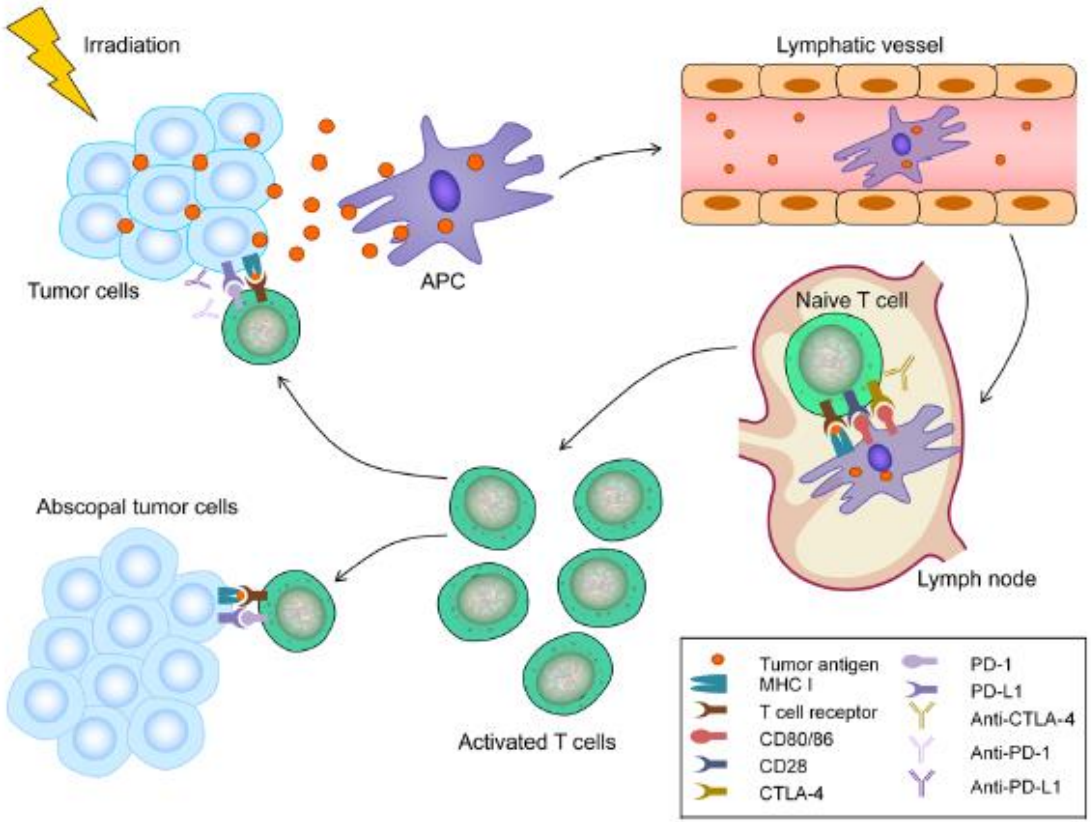


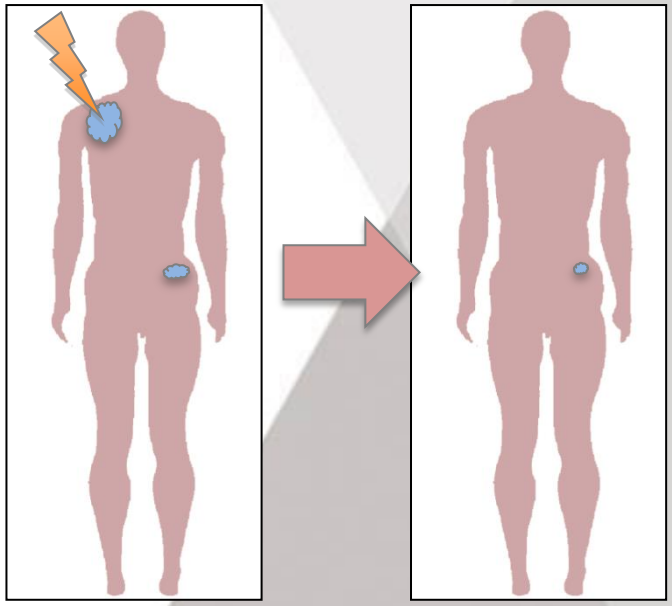
Park et al. Radiat Res 2012

Hillman et al. Radiother Oncol 2013

Perspective immunologique et fractionnement

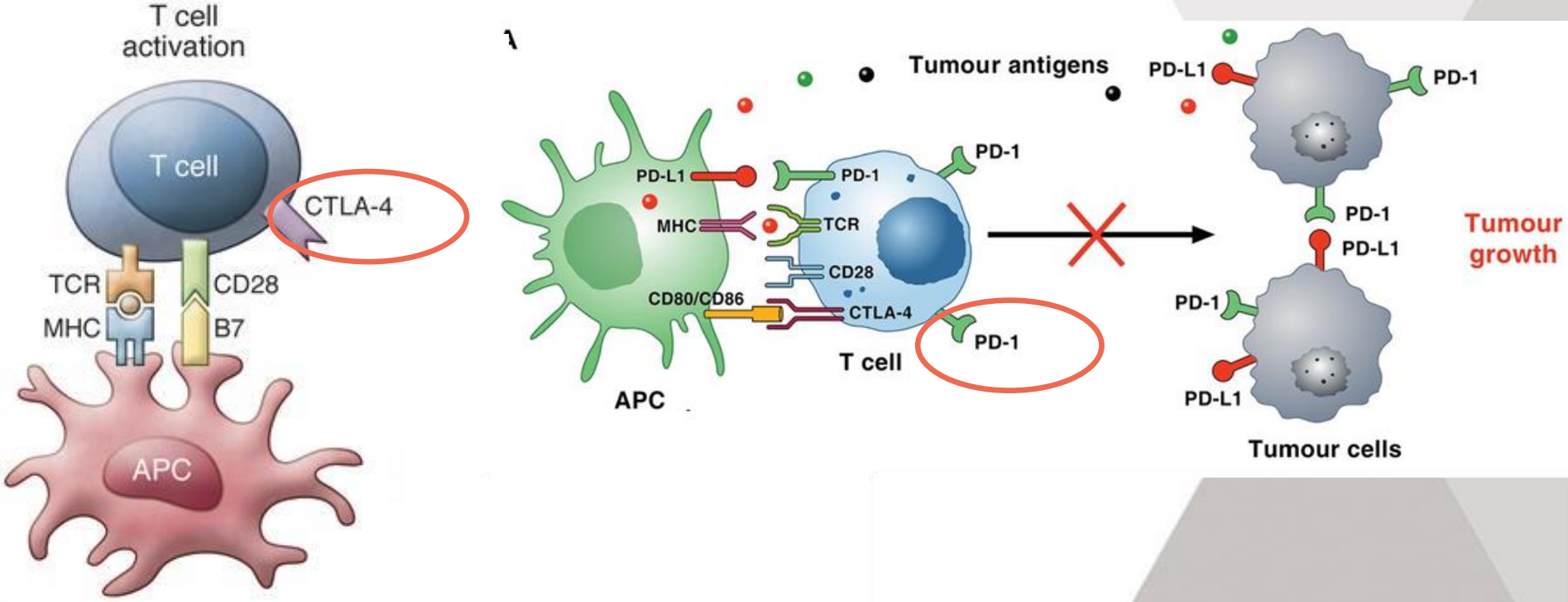
RT ➔ mort immunogénique ➔ Réponse anti-génique immunitaire adaptative





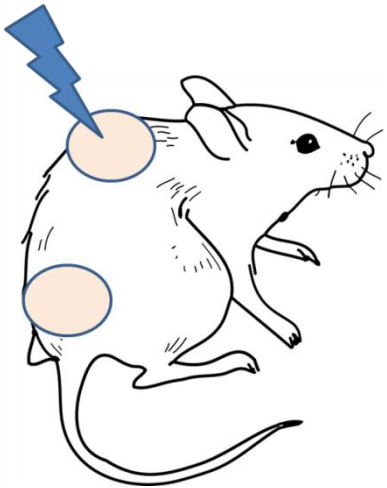
Liu et al. J. Hematol & Oncol 2018

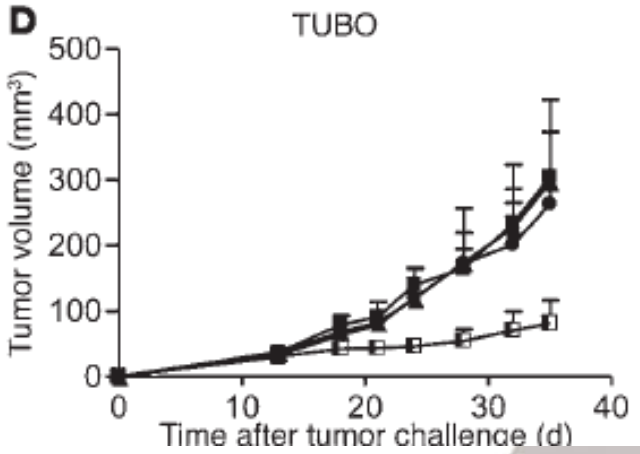
Perspective immunologique et fractionnement



Varricchi et al. ESMI Open 2017 Walker et al. Trends Immunol 2015

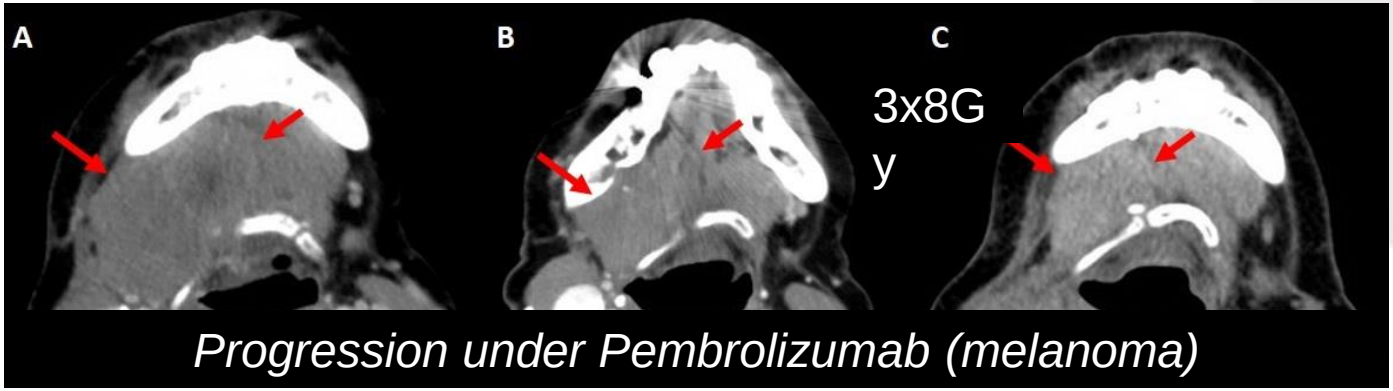
Perspective immunologique et fractionnement



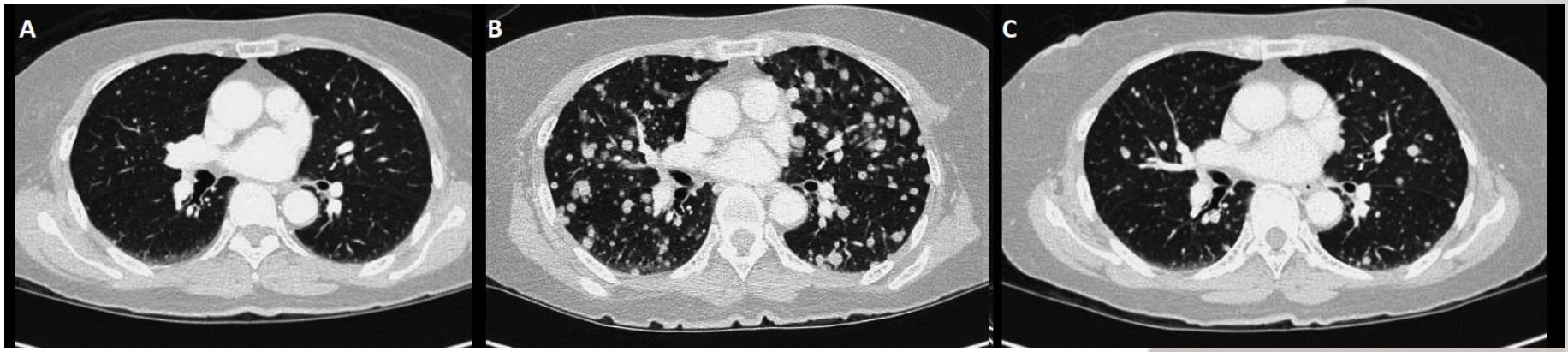


Tumor on the right flank treated
Tumor on the left flank measured

Perspective immunologique et fractionnement



Progression under Pembrolizumab (melanoma)

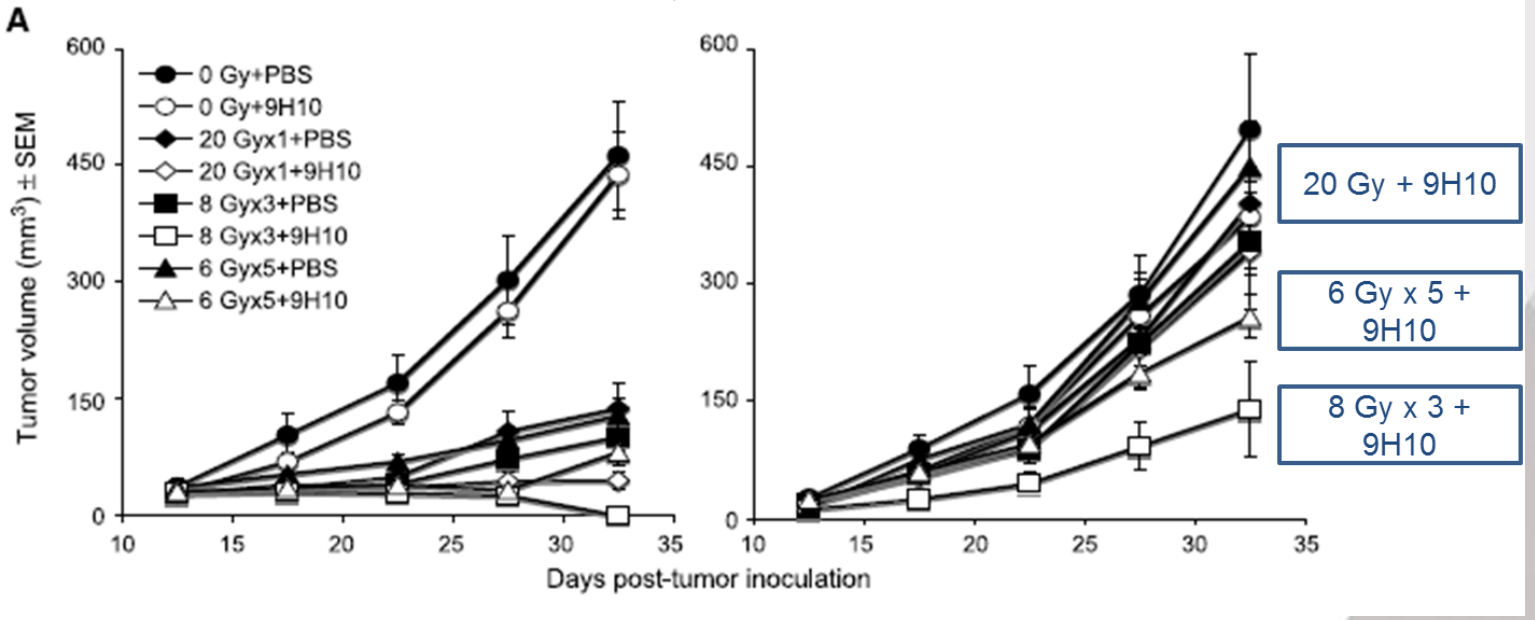


Tsui et al. . Cureus 2018

Perspective immunologique et fractionnement

Effect of dose on abscopal response with anti CTLA4

9H10 = mouse anti CTLA4 antibody



Peu de différences pour la T **irradiée**

Différences ++ pour la T **non irradiée**

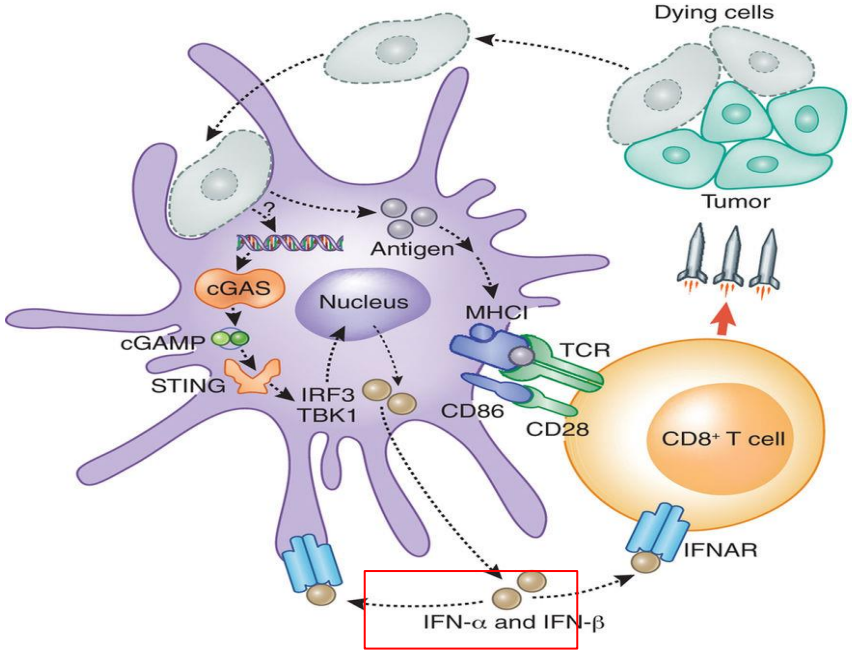
Vanpouille-Box, Nat Comm 2017

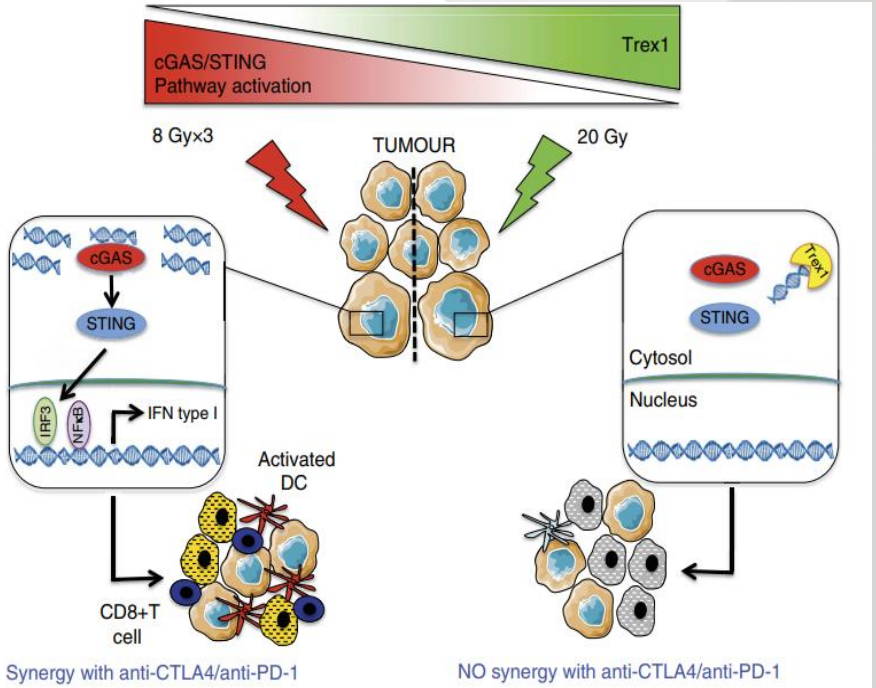
Dewan, Clin Can Res 200

Perspective immunologique et fractionnement

➔ **cGAS–STING**

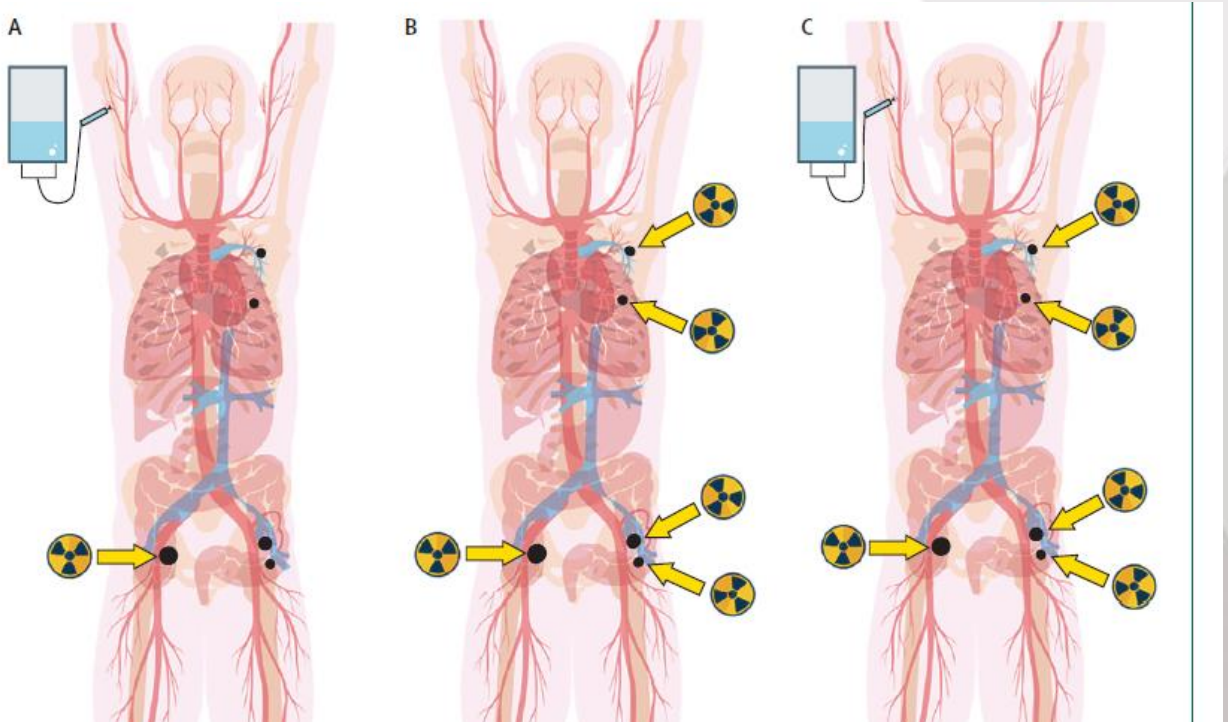
- ❖ Détecte la présence d'ADN cytosolique
- ❖ Immunité anti-tumorale via INFα/β





Chen et al. Nature Immunology 2016 Wang et al. PNAS 2017

Nouveaux concepts



Stratégies d’immuno-radiothérapie des maladies oligo-métastatiques

Deutsch et al. Lancet Oncol 2019

Synthèse

- **Hypofractionnement**
  - Outil disponible
  - Infériorité biologique (sauf cas particuliers)
  - Supériorité technologique
    - Repositionnement++
    - Marges
  - Analyse coût/bénéfice??

- **Nouveaux enjeux / perspectives biologiques**
  - Maladie oligo-métastatique, stratégies curatives
  - Radio-immunothérapie

cyrus.chargari@gustaveroussy.fr