



# Place de la radiothérapie dans la prise en charge des tumeurs rénales



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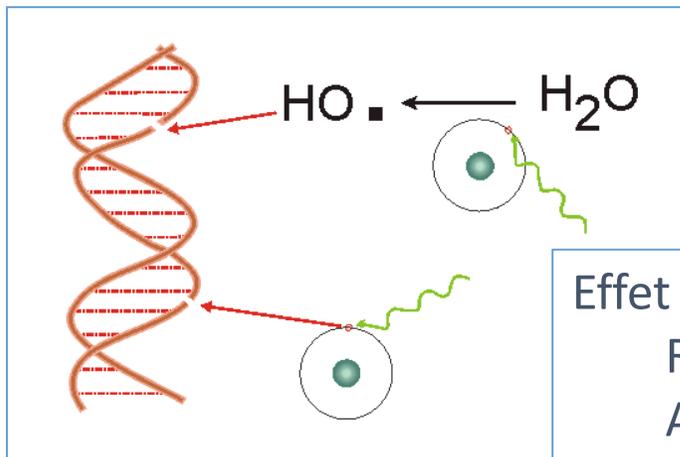
# Présentation

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- Qu'est ce que la radiotherapie ?
- Rôle de la radiothérapie dans la prise en charge des tumeurs rénales primitives
- Rôle de la radiothérapie dans la prise en charge des tumeurs rénales métastatiques

# La radiothérapie – principe général

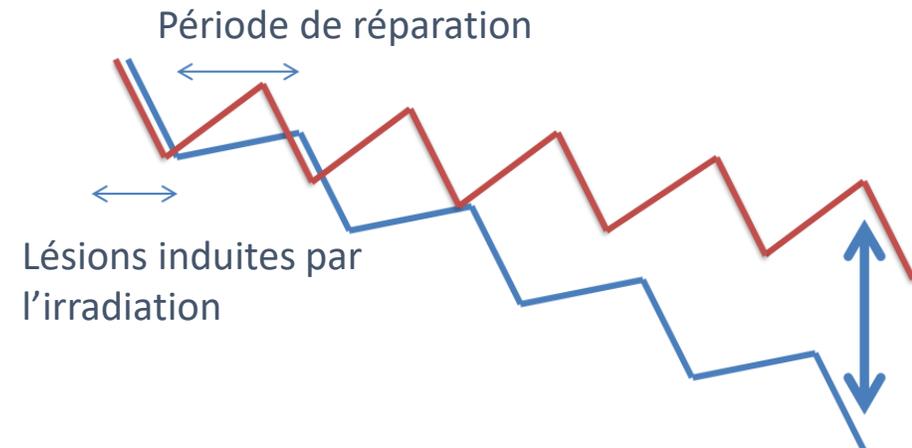
- Utilisation de radiations ionisantes à visée thérapeutique

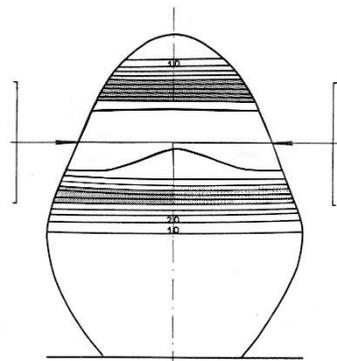
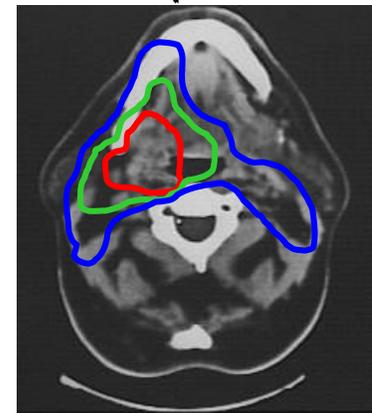
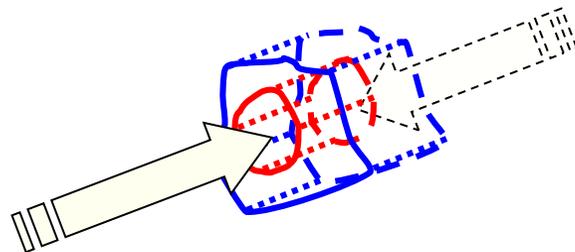
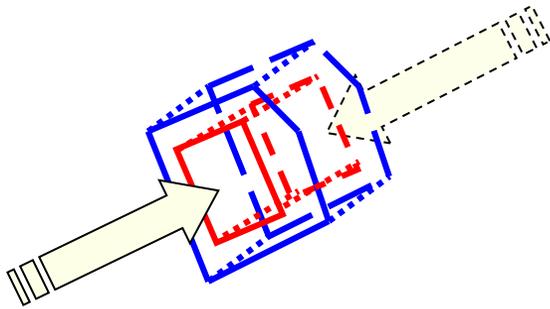
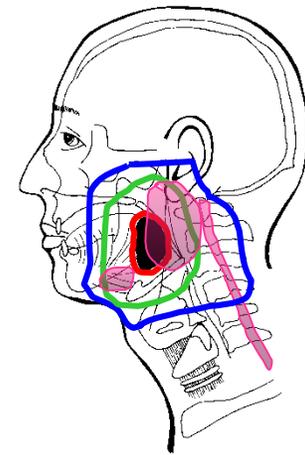
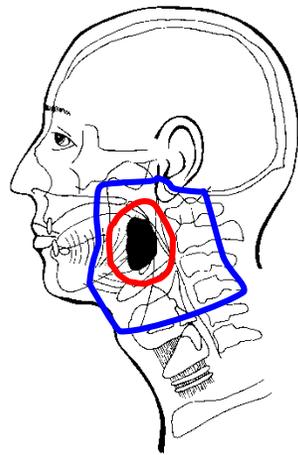
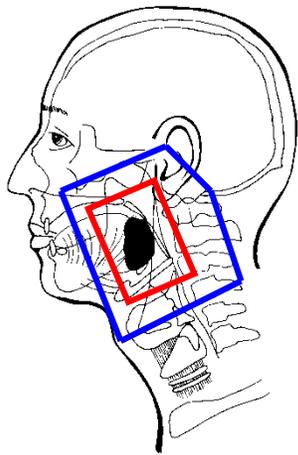


Effet indirect (majoritaire):  
Radiolyse de l'eau  
Amplifié en présence d'O<sup>2</sup>

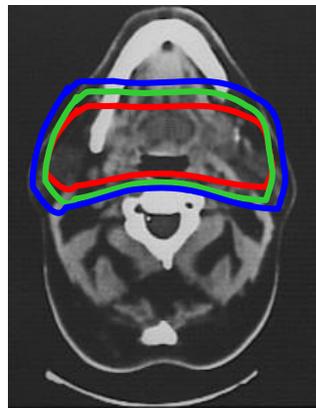
Effet direct (minoritaire):  
Lésion directe de l'A.D.N.

- L'effet biologique dépend des lésions induites par l'irradiation et de leurs réparations
- La réparation est temps dépendante

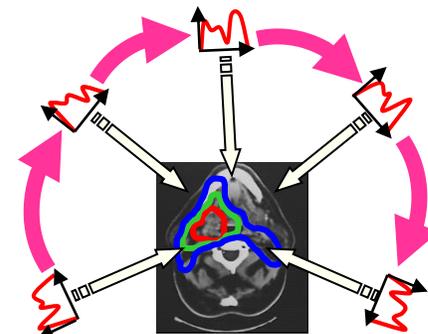
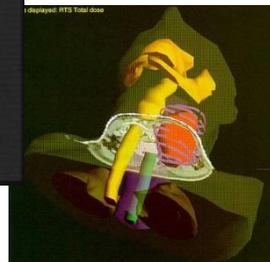




RT 2D



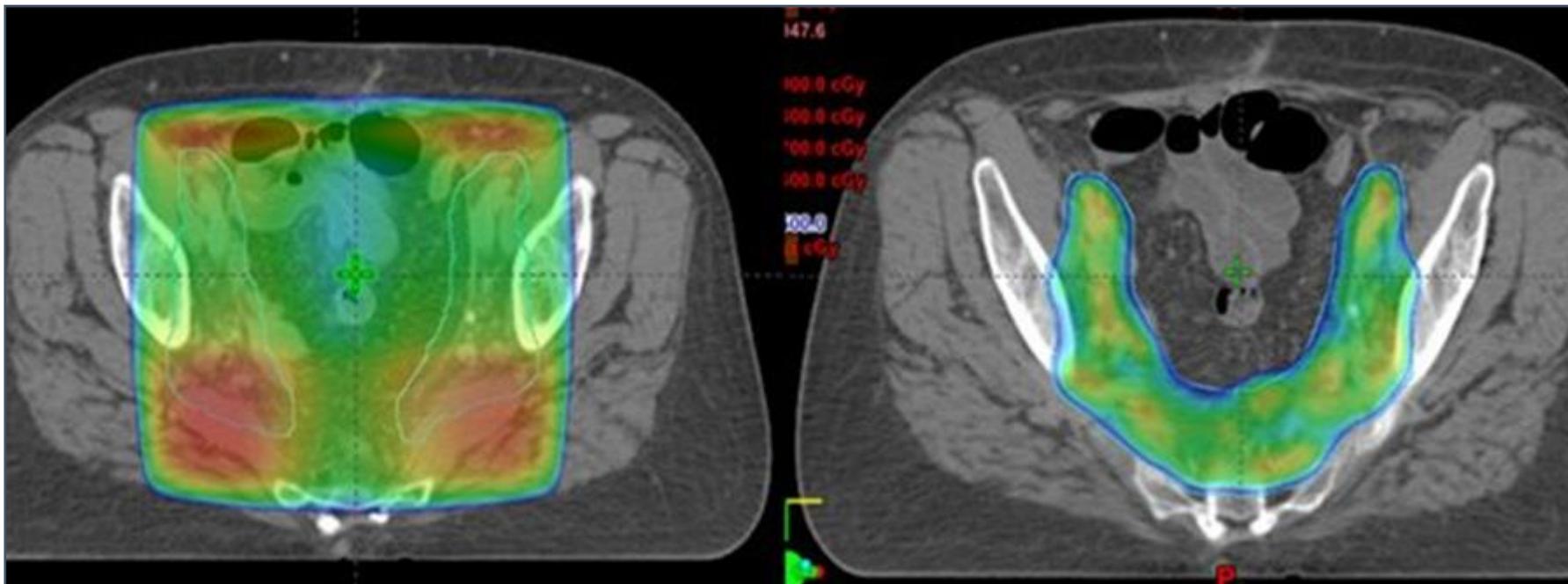
RT 3D



IMRT

# Radiothérapie avec modulation d'intensité (RCMI – IMRT)

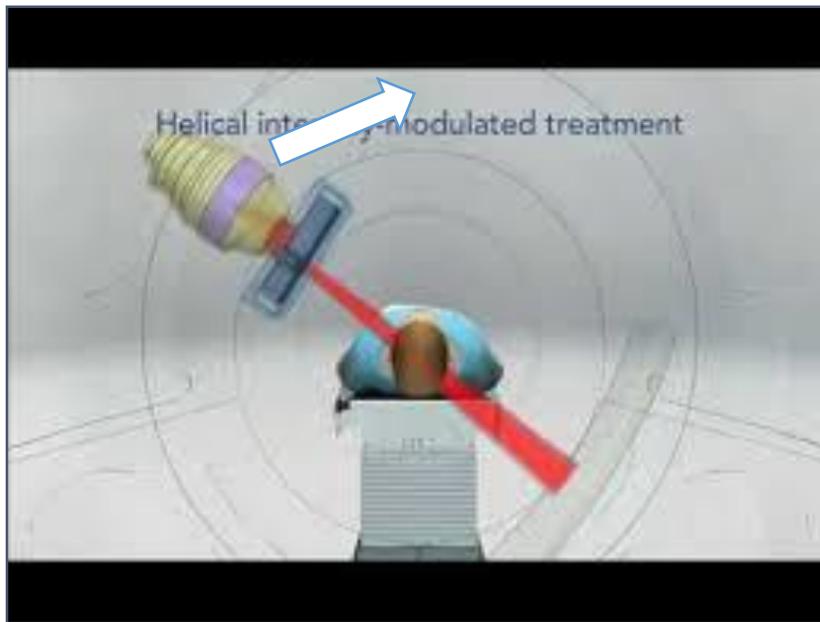
- Meilleure conformité du traitement



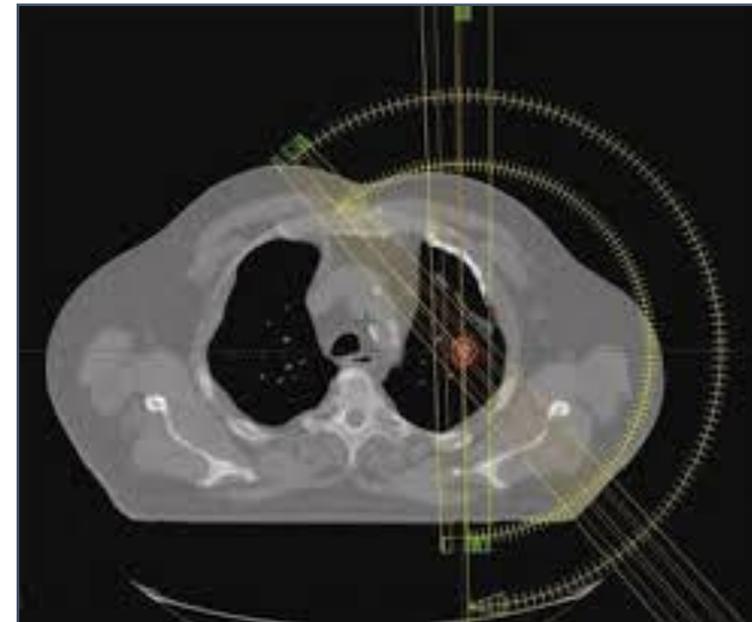
Dosimétrie avec et sans modulation d'intensité

# Radiothérapie rotationnelle

- Rotation de la tête de l'irradiateur externe permettant de multiplier les incidences



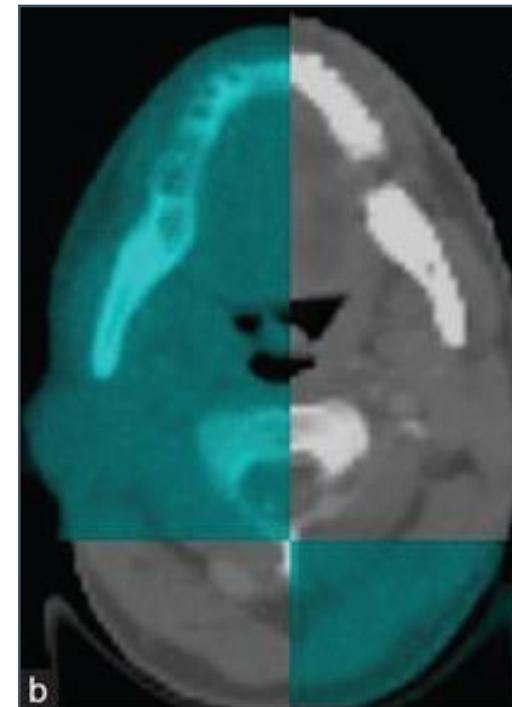
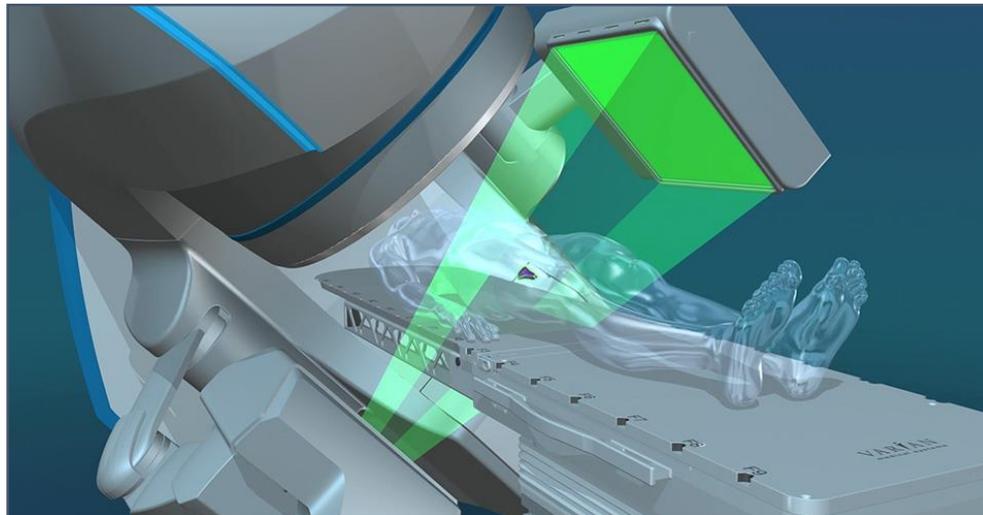
Rotation en cours d'irradiation



Arctherapie

# Radiothérapie guidée par l'image

- Plus de conformation nécessite plus de précision



Repositionnement par imagerie pré-thérapeutique

# Radiothérapie en conditions stéréotaxiques



Accélérateur avec  
collimateurs micro multi-  
lames et IGRT  
**(Novalis)**

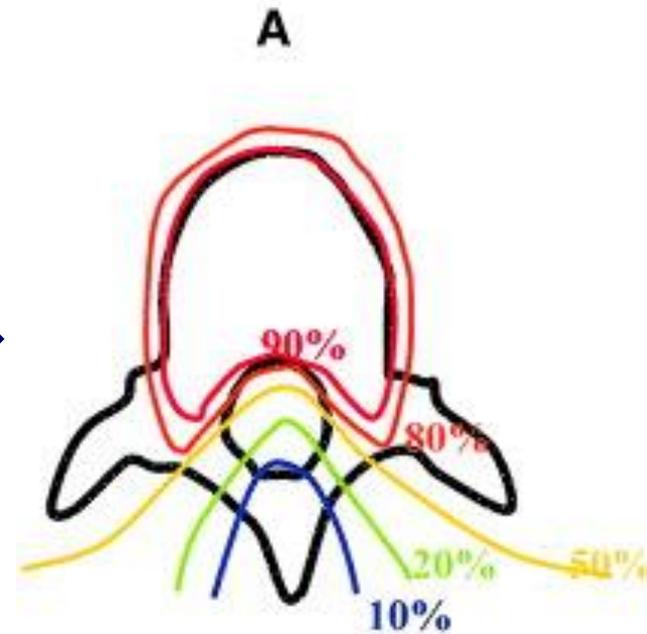
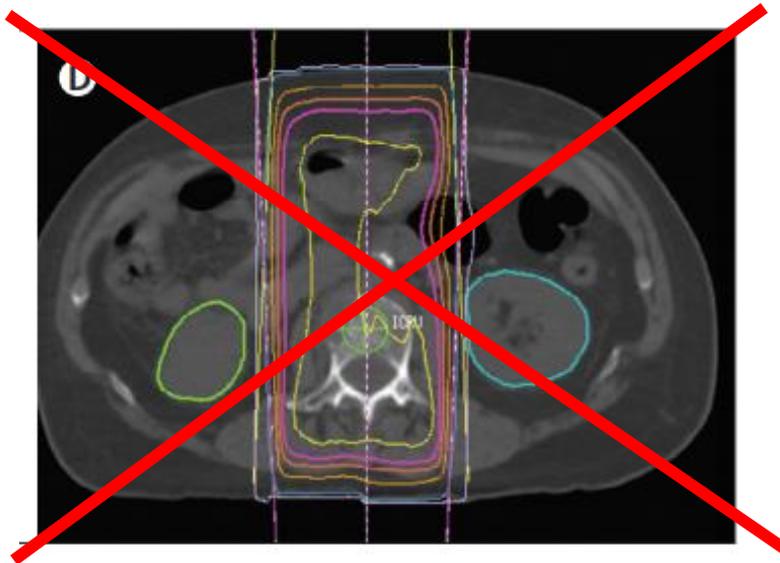


Machine dédiée  
stéréotaxie  
**(Cyberknife)**

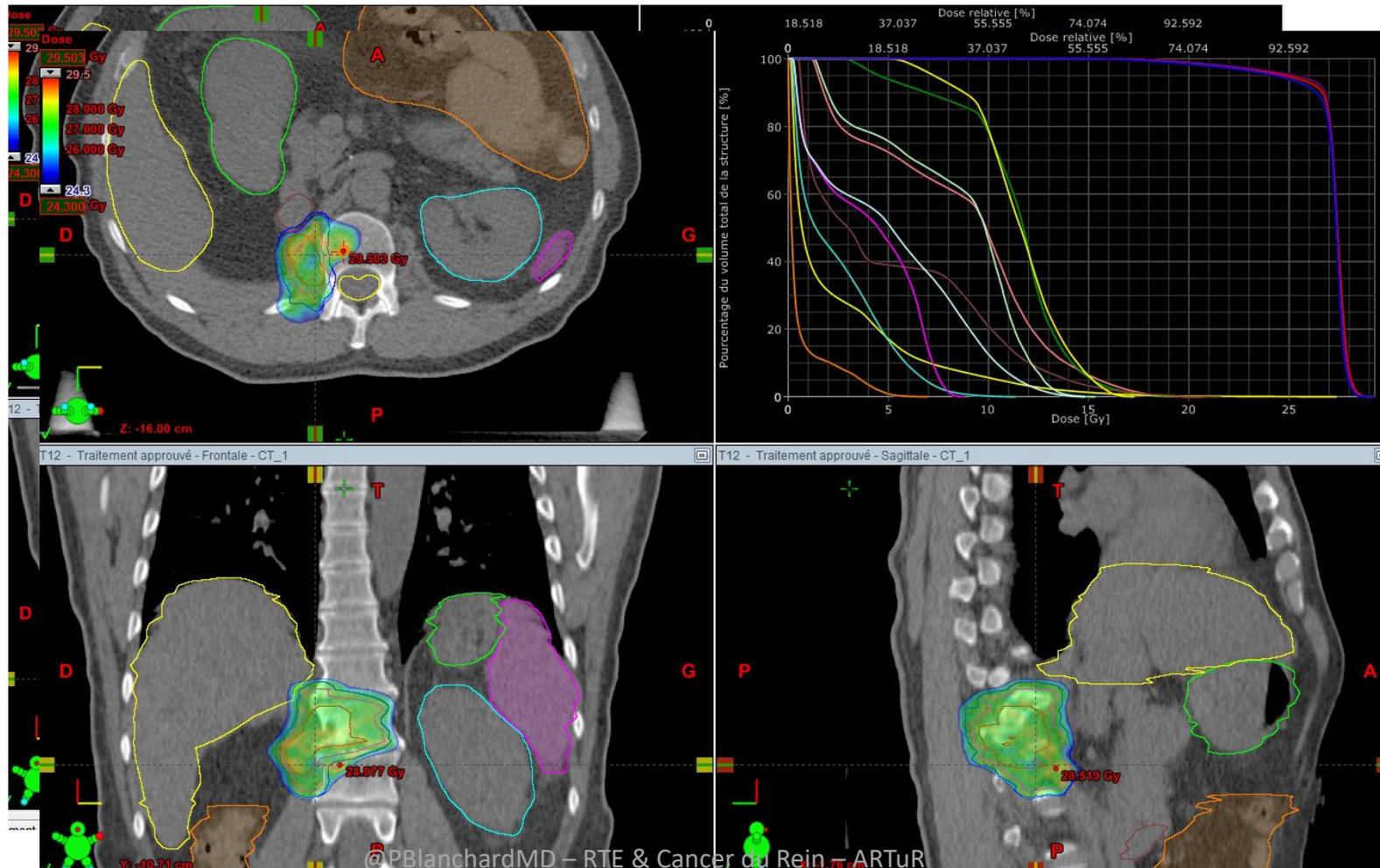
Utilisée pour des lésions primitives et secondaires de petite taille  
(cerveau, os, poumon, foie, et autres)

# Radiothérapie en conditions stéréotaxiques

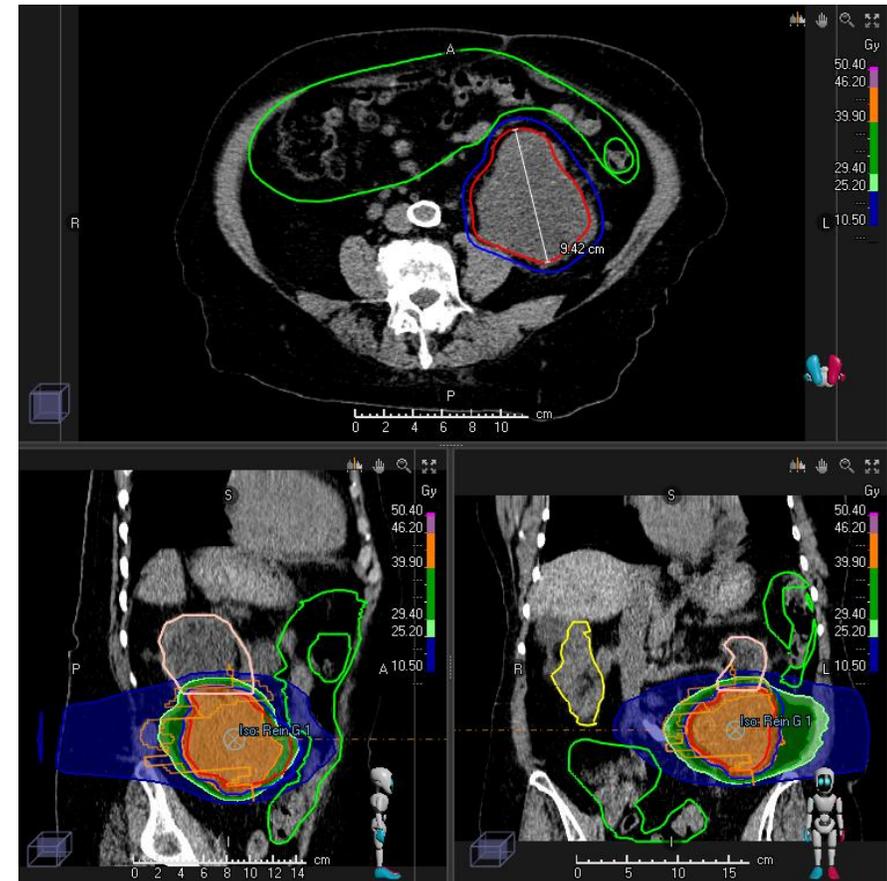
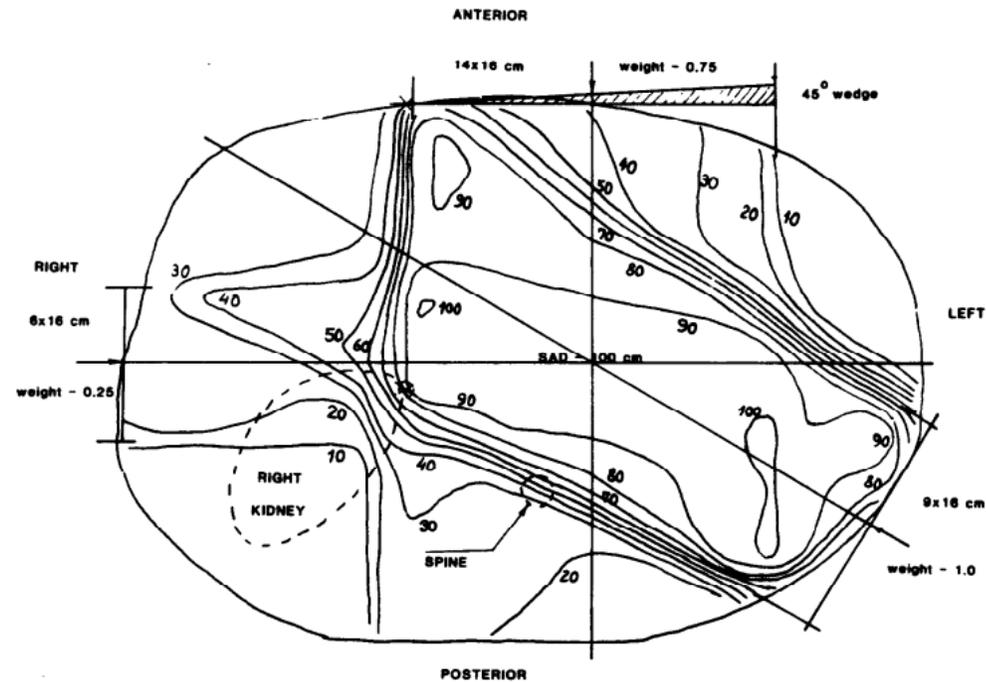
- Passage de la 3D à une irradiation hautement conformationnelle – nécessité d'importants gradients de dose



# Exemple d'irradiation en conditions stéréotaxique – cancer médullaire rénal avec métastase T12 en progression après cryothérapie



# En pratique pour les tumeurs rénales : le passage à la stéréotaxie...



- Une radiorésistance *in vitro*

Tumor cell lines	Fibroblastic and normal cell strains	n	D		S2	
			Mean (Gy)	CV (%)	Mean	CV (%)
Stomac cancer		2	2.79	27	0.58	24
Glioblastoma		7	3.10	41	0.58	36
Bladder carcinoma		5	3.22	6	0.63	8
Ewing's sarcoma		1	3.27	—	0.65	—
Renal cell carcinoma	Kidney	1	3.29	—	0.67	—
		1	4.80	—	0.81	—

Cell types are ranked by increasing values of  $\bar{D}$ , \*(fib) = fibroblast.

*Deschavanne et Fertil et al. Cancer 1997*

Classification of human tumours according to clinical radioresponsiveness.

- A. Neuroblastoma, lymphoma, myeloma
- B. Medulloblastoma, small-cell lung carcinoma
- C. Breast, bladder, cervix carcinoma
- D. Pancreas, colo-rectal, squamous lung carcinoma
- E. Melanoma, osteosarcoma, glioblastoma, renal carcinoma

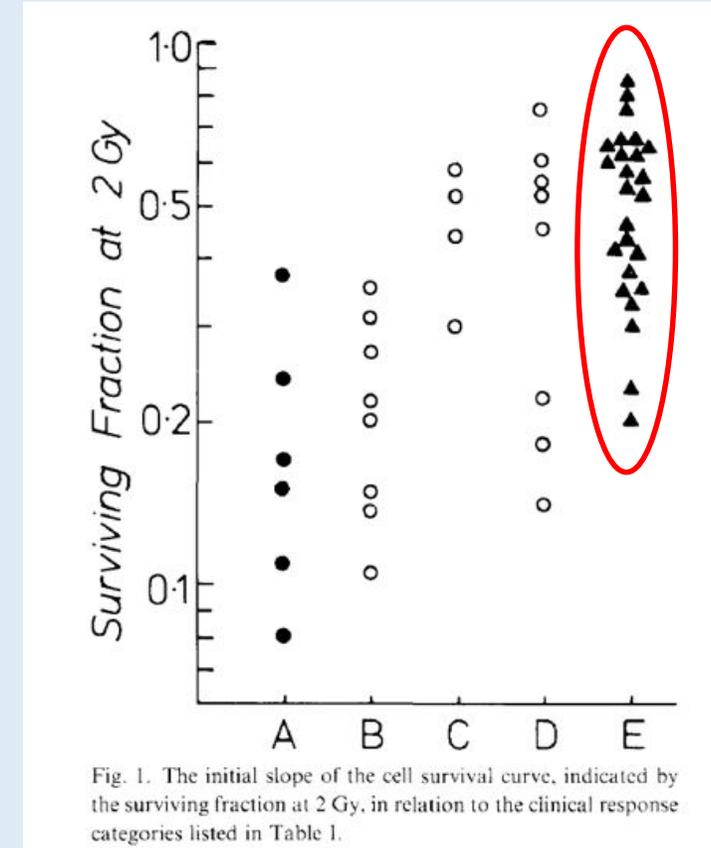
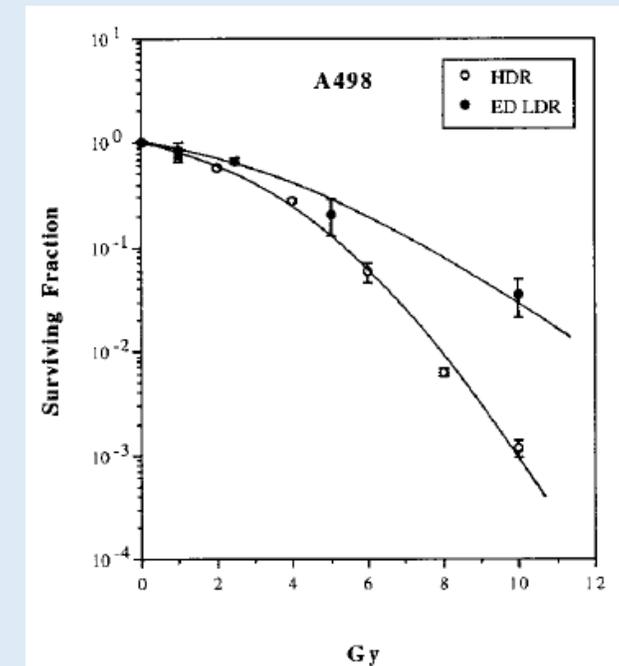
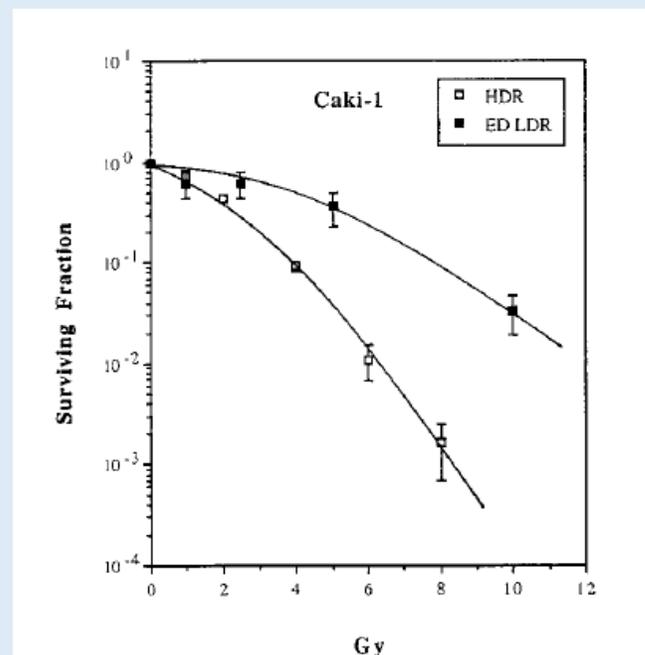
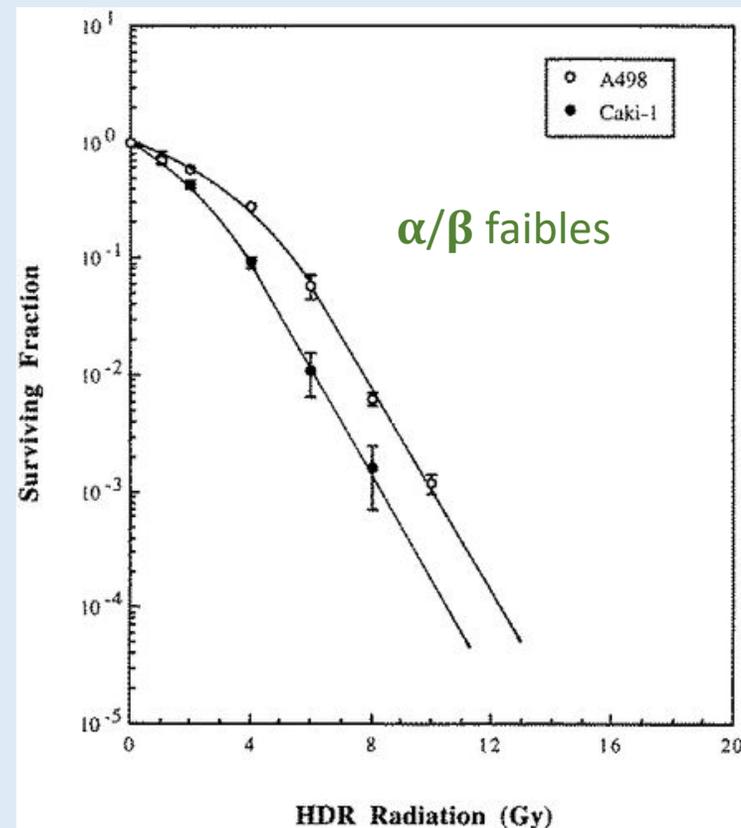


Fig. 1. The initial slope of the cell survival curve, indicated by the surviving fraction at 2 Gy, in relation to the clinical response categories listed in Table 1.

*Deacon et al. Radiother Oncol 1984*

- Mais une possible radiocurabilité avec l'augmentation de la dose ?

Radiobiologic Studies of Radioimmunotherapy and External Beam Radiotherapy In Vitro and In Vivo in Human Renal Cell Carcinoma Xenografts

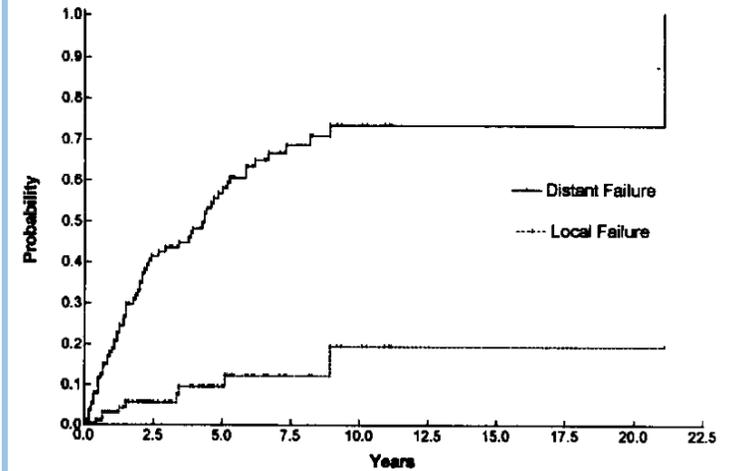


Influence de la dose et du débit de dose

- Survie après néphrectomie +/- RTE adjuvante = 2 essais prospectifs randomisés

R1, infiltration VCI, +/- pN+

Study	Stage	No. of Patients	Radiation Dose/Fraction Size (Gy)	Treatment	5-Yr Survival Rate (%)	Local Recurrence (%)	RT-related Mortalit (%)
Fugitt, 1973 <sup>112</sup>	NS	48	—	N	47	7	18
		52	55/2.04	N + ART	(17/35) 36 (14/39)	7	
Kjaer et al., 1987 <sup>64</sup>	II, III	33	—	N	63 <sup>a</sup>	1	19
		32	55/2.5	N + ART	38 <sup>a</sup>	0	

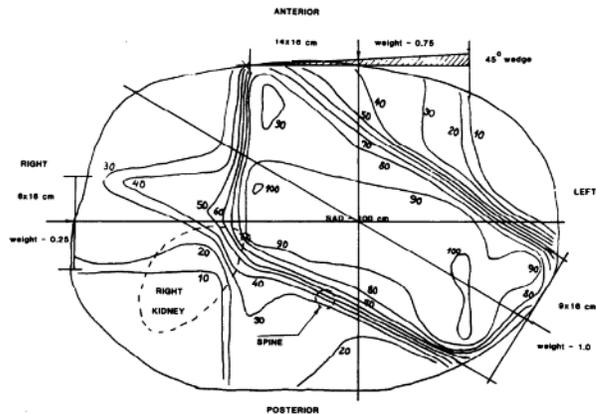


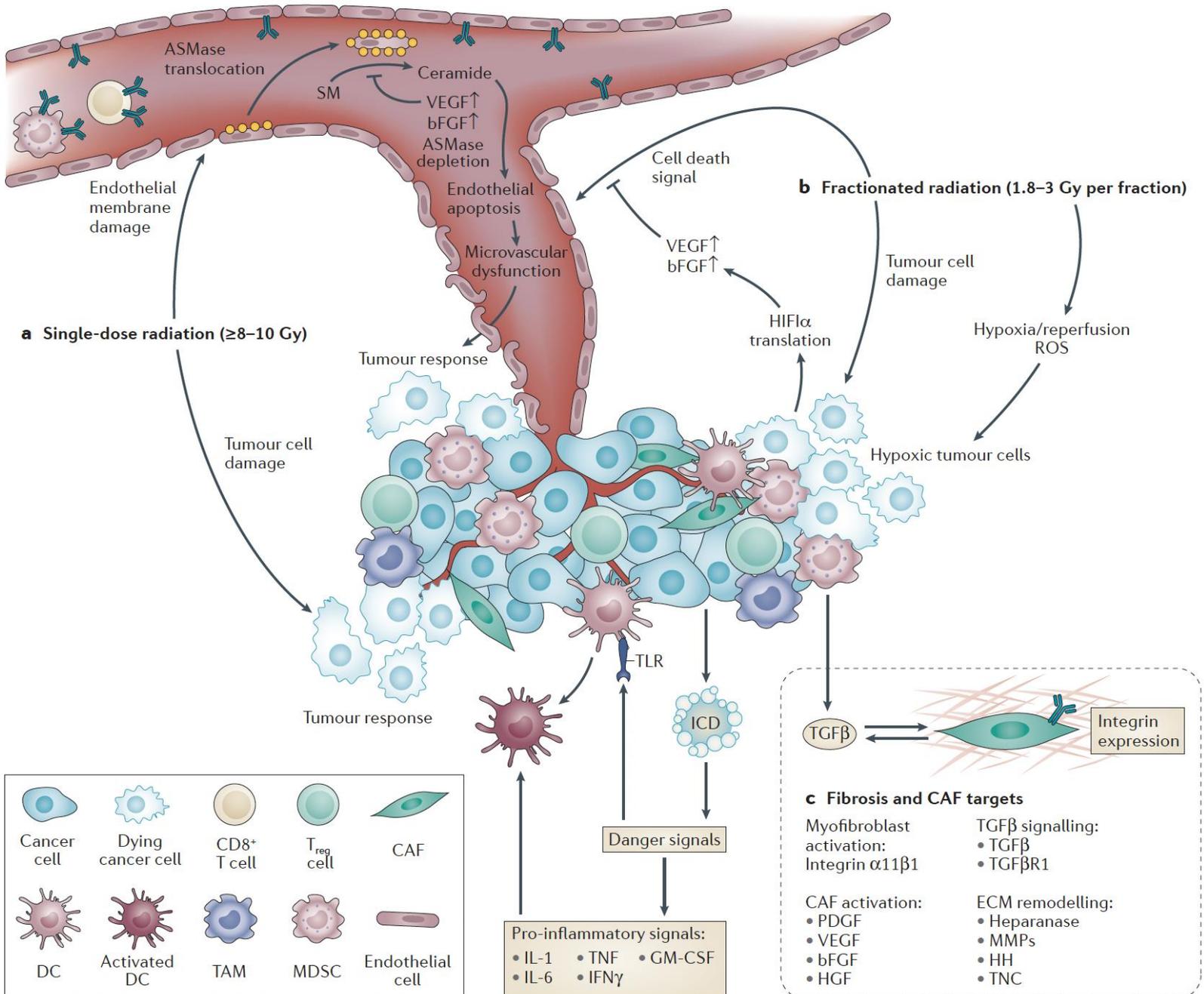
*Aref et al. Radiother Oncol 1997*

**Aucun avantage en survie ni en contrôle local**  
**Risque majoré de mortalité (toxicités digestives ++)**

**Principal pattern de rechute après**

**NE = à distance**





**1 EFFET VASCULAIRE**

Apoptose des cellules endothéliales

**2 EFFET IMMUNOLOGIQUE**



**CANCER RENAL = modèle IDEAL pour le développement de la SBRT**

# Présentation



- Qu'est ce que la radiotherapie ?
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- Rôle de la radiothérapie dans la prise en charge des tumeurs rénales métastatiques

## Critères de sélection

### PATIENTS



- Inopérables ou risque de dialyse si chirurgie
- Clairance > 25-30 mL/min

### TUMEURS



- Pas de critère de taille
- **Toute localisation** dans le rein
- Possibilité si rein unique ou tumeurs bilatérales
- Preuve histologique préalable

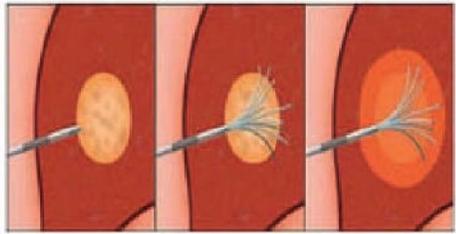
### Advantages

- Can be administered as an outpatient treatment
- Safe and minimally toxic
- Provides promising local control rates
- No definite size limitations
- Not limited by tumour location
- Might stimulate or promote antitumour immunity
- Suitable for patients with surgically unresectable tumours
- Feasible in patients with a functionally solitary kidney

### Disadvantages

- Does not enable tissue sampling for histological confirmation
- Limited prospective evidence for outcomes
- Safe lower limit of renal function pre-SABR remains undefined
- Optimal dose and fractionation regimen remains undefined
- Ideal treatment response assessment modality not yet established
- Very stringent technical and quality assurance requirements
- Requirement of intensive training of the whole radiotherapy team

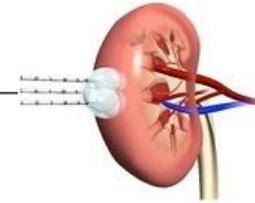
## RADIOFREQUENCE



∅ < 4 cm

Difficulté si lésion/cavités urinaires

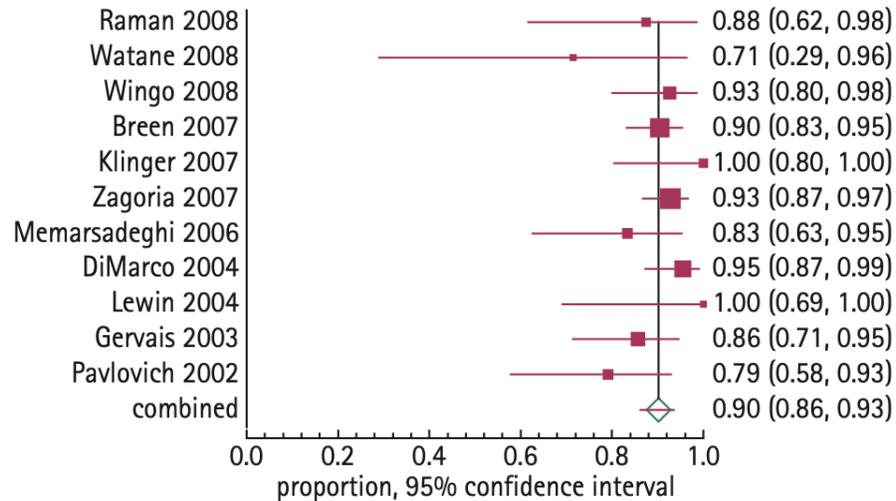
## CRYOABLATION



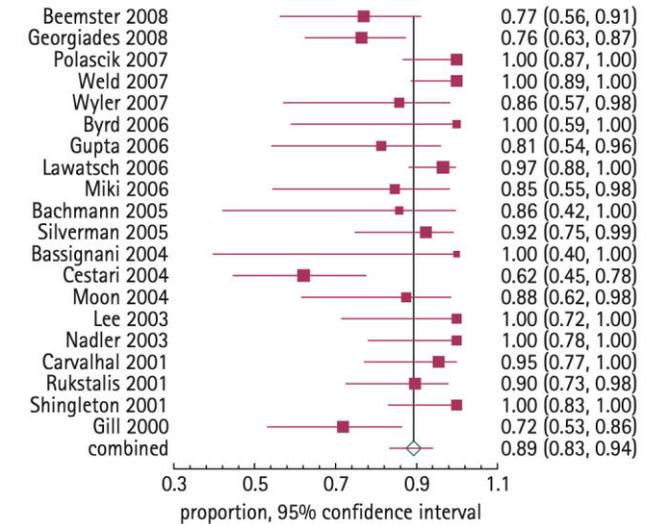
Moins de restriction sur la taille

Difficulté si lésion/cavités urinaires

Proportion meta-analysis plot [random effects]



Proportion meta-analysis plot [random effects]



*El Dib et al. BJUI 2012*

- RFA, MWA or CA are options in patients with small cortical tumours  $\leq 3$  cm, frail patients, high surgical risk, solitary kidney, compromised renal function and hereditary RCC or bilateral tumours [III]

## MUTLI FRACTION

auteur	effectif	suivi médian (mois)	Average marginal dose (Gy)	Contrôle local (brut)	Contrôle local à 2 ans	Toxicités >G2
Chang et al. 2016	16	19	30-40Gy en 5 fractions	100%	NR	2 G4 tardives
Gilson et al. 2006	33	17	Médiane 40Gy en 5 fractions	94%	92	NR
McBride et al. 2013 (abstract) [prosp.]	15	36,7	Médiane 33Gy en 3 fractions	87%	NR	1 G3 tox rénale
Qian et al. 2003 (abstract)	20	12	40Gy en 5 fractions	93%	86	NR
Ponksy et al. 2015 [prosp.]	19	13,7	Max 48Gy en 4 fractions	NR	NR	15,8% 3-4

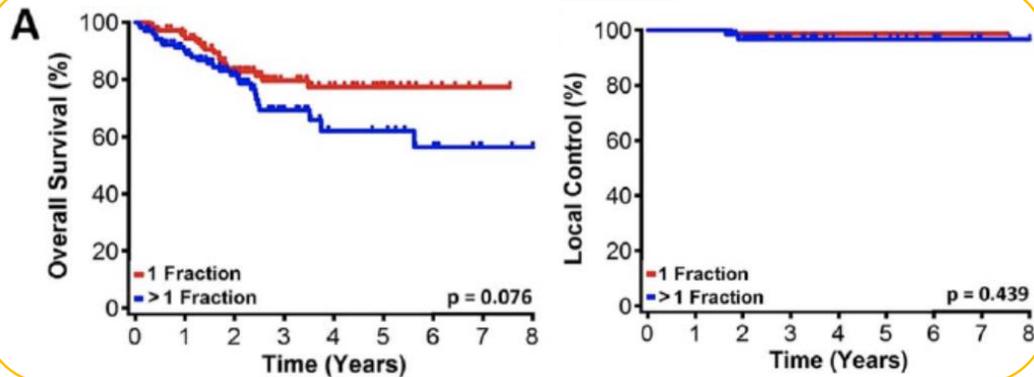
## FRACTION UNIQUE

Pham et al. 2014 [prosp.]	20	6	<b>26Gy en 1 fraction</b> <b>42Gy en 3 fractions</b>	NR	NR	0 G3-4
Siva et al. 2017 [prosp.] <b>FASTRACK trial</b>	33	24	<b>26Gy en 1 fraction (&lt;5cm)</b> <b>42Gy en 3 fractions (&gt;5cm)</b>	<b>97%</b>	100%	3% G3
Staehler et al. 2015 [prosp.]	40	28,1	<b>25Gy en 1 fraction</b>	<b>98% (at 9mo)</b>	NR	0 G3-4

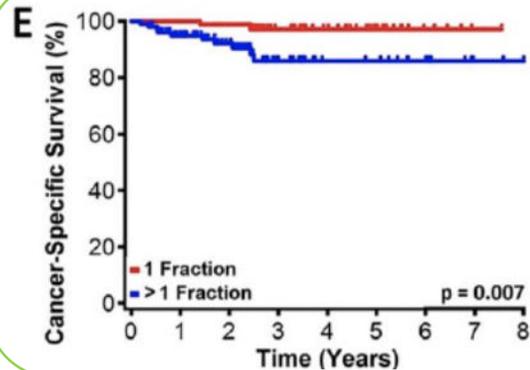
# Stéréotaxie rénale: quel impact du fractionnement ?

## Pooled Analysis of Stereotactic Ablative Radiotherapy for Primary Renal Cell Carcinoma: A Report From the International Radiosurgery Oncology Consortium for Kidney (IROCK)

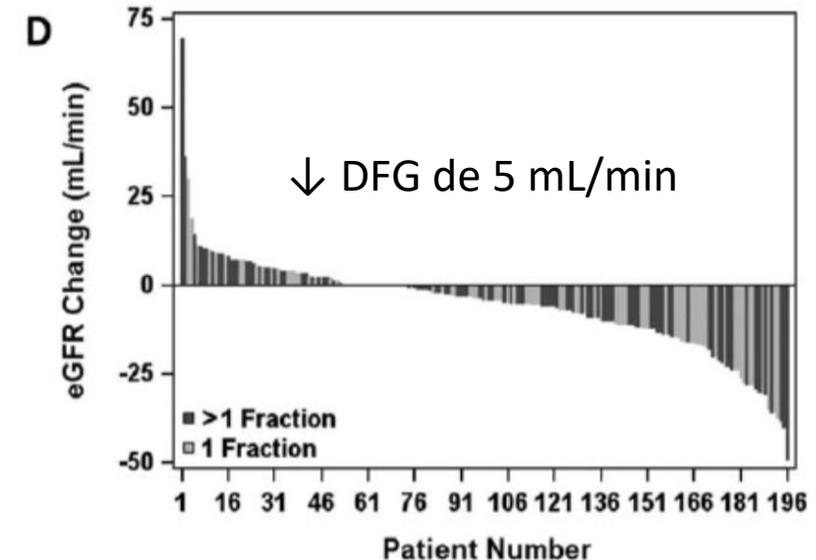
- Analyse multicentrique
- n=223: **118 une fraction / 105 multi-fractions**
- Patients 1 seule fraction : plus jeunes, meilleur OMS, tumeurs plus petites (4 cm)
- BED<sub>10</sub> identique



Contrôle local et survie globale similaires

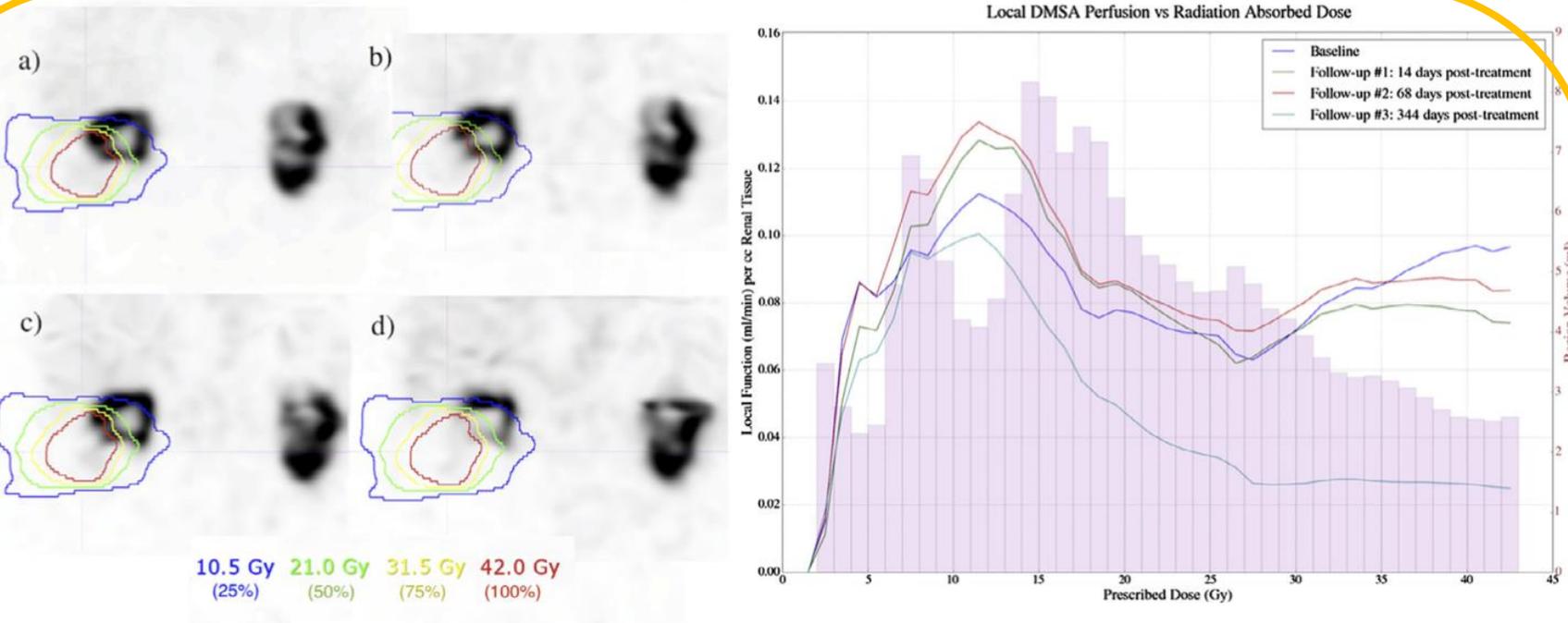


Meilleure survie  
spécifique dans le groupe  
1 fraction

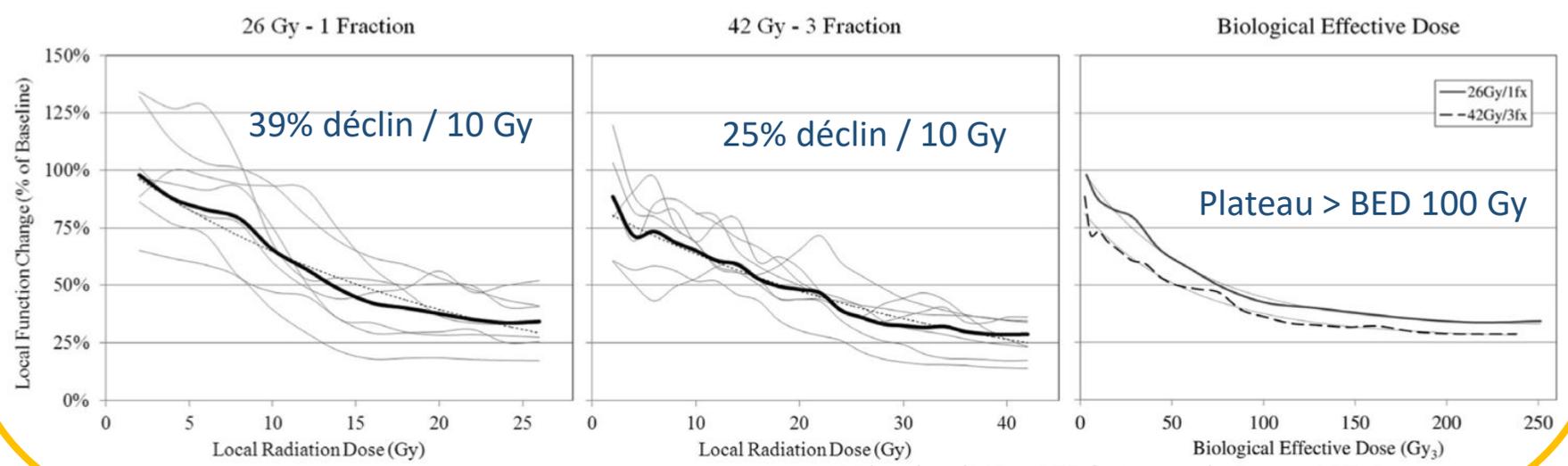


Pas de différence sur variations DFG

# Impact de la stéréotaxie sur la fonction rénale



- Perte de fonction glomérulaire dose-dépendante à 1 an
- Corrélation index de conformité R50% avec baisse GFR (p=0,04)



➡ **SBRT induit une BAISSSE DU GFR**

# Présentation

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**Table 1. Summary of articles using SBRT to primary kidney in mRCC**

Authors	Number of patients	Median age	IMDC group (%)	Histology	Median size, cm	Radiation dose (Gy)/fraction	Local control	Overall survival	Median followup (months)
Singh et al, 2017	14 <sup>a</sup>	64	Intermediate: 13 Poor: 1	Clear-cell: 12 Chromophobe: 1 Papillary urothelial: 1	Not reported	15/1	Not reported	1-year: 71% 2-year: 48% Median: Not reported	Not reported
Correa et al, 2018 – prospective	12 <sup>b</sup>	67	Favorable: 1 Intermediate: 8 Poor: 3	Clear-cell: 9 Papillary: 2 Poorly differentiated carcinoma: 1	8.7	25/5: 3 30/5: 6 35/5: 3	100%	1-year: 38% 2-year: 19% Median: 6.7 months	5.8
Correa et al, 2018 – retrospective	11 <sup>c</sup>	79	Intermediate: 6 Poor: 5	Clear-cell: 5 Spindle-cell: 1 Undifferentiated: 1 Unknown: 4	9.5	25/5: 6 30/5: 3 35/5: 1 40/5: 1	85% <sup>d</sup>	1-year: 53% 2-year: 53% Median: 20.4 months	46.8

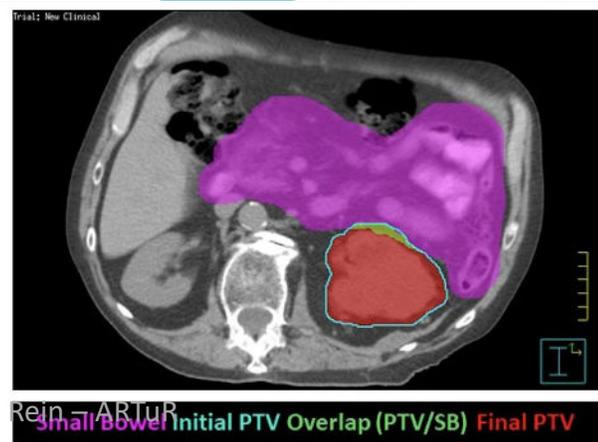
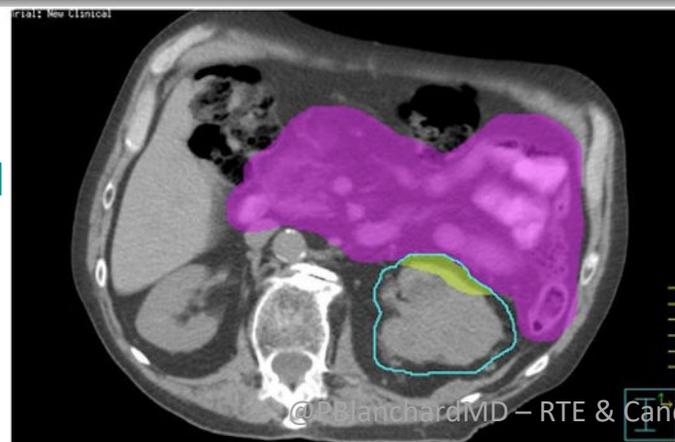
**TOX G3**

6%

25%

9%

Étude Correa 2018 : SBRT « néphrectomie-like »

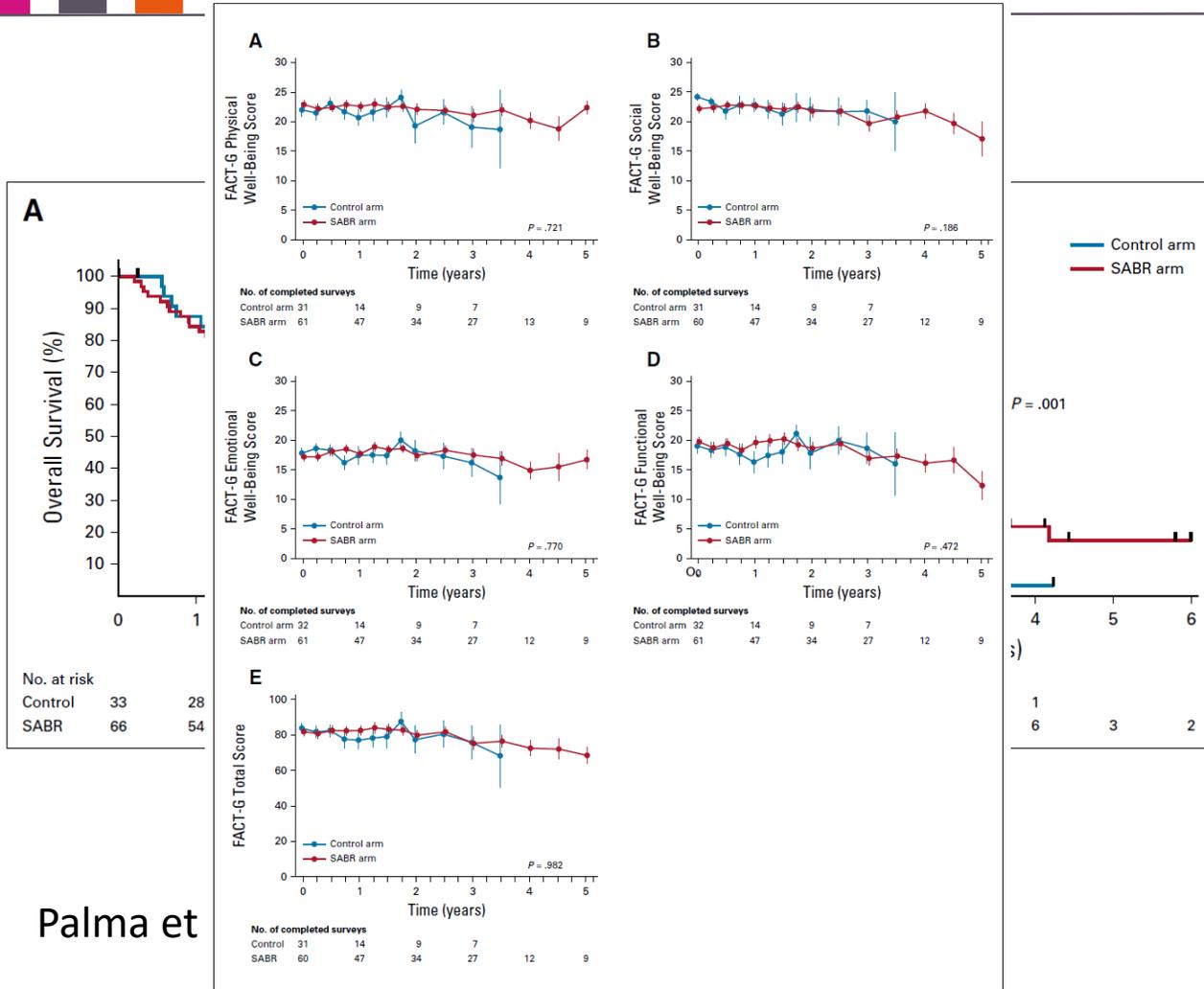


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# Intérêt de la radiotherapie des patients oligométastatiques (tumeur primitive contrôlée)

TABLE 1. Baseline Characteristics

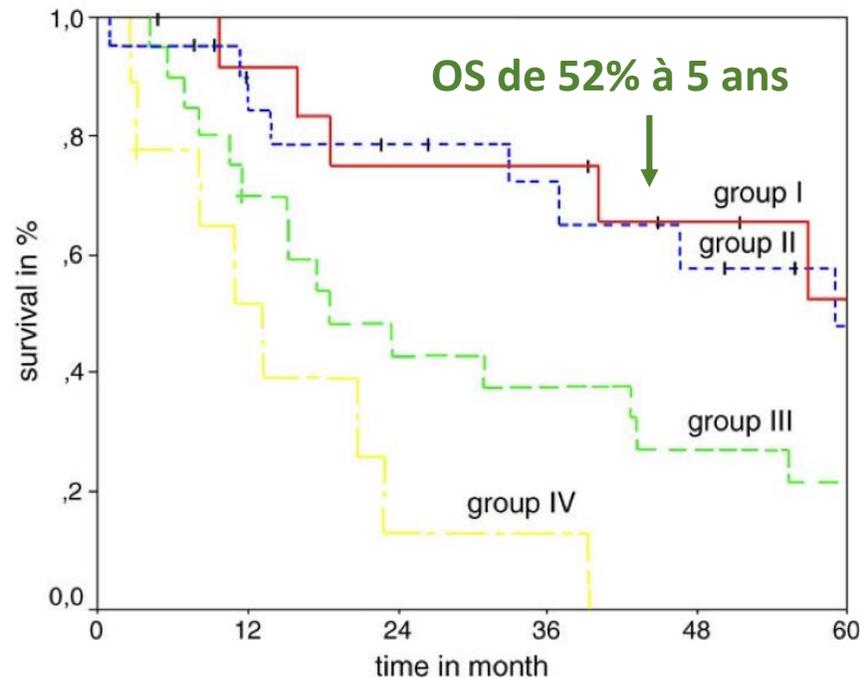
Characteristic	Arm, No. (%)	
	Control (n = 33)	SABR (n = 66)
Median age, years (IQR)	69 (64-75)	67 (59-74)
Sex		
Male	19 (58)	40 (61)
Female	14 (42)	26 (39)
Site of original primary tumor		
Breast	5 (15)	13 (20)
Colorectal	9 (27)	9 (14)
Lung	6 (18)	12 (18)
Prostate	2 (6)	14 (21)
Other	11 (33)	18 (27)
Median time from diagnosis of primary tumor to random assignment, years (IQR)	2.3 (1.3-4.5)	2.4 (1.6-5.3)
No. 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 (n = 191 lesions)		
Adrenal	2 (3)	7 (6)
Bone	20 (31)	45 (35)
Liver	3 (5)	16 (13)
Lung	34 (53)	55 (43)
Other <sup>a</sup>	5 (8)	4 (3)



Palma et

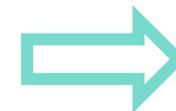
20-40% des patients développent une maladie M+ après néphrectomie (foie > poumons)

### Métastasectomie de lésions pulmonaires



	Hazard ratio	95% CI	<i>p</i>
Age			
≤60 years			
>60 years	0.06	0.5–1.7	0.8
DFI			
Metachronous			
Synchronous	7.8	1.5–11.5	<b>0.005</b>
Location			
Unilateral			
Bilateral	1.2	0.72–3.4	0.25
Number			
Solitary			
Multiple	5.4	0.16–0.83	<b>0.02</b>
R-status			
R0			
R1/R2	11.1	0.1–0.5	<b>0.001</b>

Avantage en survie en cas de métas métachrones  
et nombre réduit de métas



**SELECTION des patients**



Study (n = number of patients)	Metastases (% of patients)	Marginal dose (Gy)	Outcomes	Toxicities
Cochran <i>et al.</i> (2012) <sup>119</sup> n = 61	Brain: 46%; extracranial: 90%	Median 20 (13–24)	1-year local control 93%; median OS duration 9 months; 1-year OS rate 38%, after a median follow-up duration 9 months*	Radiation-induced oedema or necrosis in 10% of patients; haemorrhage in 3% of patients
Fokas <i>et al.</i> (2010) <sup>120</sup> n = 68	Brain: 62%; extracranial: 32%	Median 19 (15–22)	Crude local control 75% <sup>‡</sup> ; 1-year local control 83%*	Grade ≥3 acute toxicities in 3% of patients receiving SRS only; in 3% of patients receiving SRS + WBRT; grade 3 late-onset toxicities in 4% of patients receiving SRS only, 5% (2/68) with SRS + WBRT, overall 6% late-onset toxicities
Ippen <i>et al.</i> (2015) <sup>90</sup> n = 66	Brain: 59%; extracranial: 96%	22 in 1 fraction (12–30 Gy in 1–5 fractions)	Crude local control 93% in SRS group, 94% in SRS + surgery group, 88% in SRS + WBRT group; 1-year local control 84% in SRS group; median OS duration 13.9 months; 1-year OS rate 55% after a median follow-up duration of 10 months	Acute grade ≥3 toxicities in 4.5% of patients; late-onset grade ≥3 toxicities in 1.5% of patients
Janssen <i>et al.</i> (2015) <sup>125</sup> n = 36	Brain: 56%; extracranial: 61%	Range from 16–23	NR	NR
Kano <i>et al.</i> (2011) <sup>93</sup> n = 158	Brain: 51%; extracranial: 77%	Median 18 (10–22)	Crude local control 91%; 1-year local control 87%; median OS duration 8 months; 1-year OS duration 38% after a median follow-up duration of 8 months*	Symptomatic adverse effects observed in 7% of patients; tumour haemorrhage observed in 6% of patients; of note, clinical follow up data were only available from 108/158 patients
Seastone <i>et al.</i> (2014) <sup>91</sup> n = 166	Brain: 76%; extracranial: NR	Modal 24 (12–35)	Crude local control 90%; 1-year local control 75%	NR
Shuto <i>et al.</i> (2010) <sup>132</sup> n = 105	NR	Mean 22 (8–30)	Crude local control 84%; 1-year local control 71%*; median OS duration 12 months after a median follow-up duration of 7 months*	2% of patients had haemorrhage requiring surgery; 5% of patients had peritumoural oedema

## MESSAGES CLES

- Un recul > 20 ans
- > 1300 patients, > 3400 lésions
- **Taux de CL = 93%**
- OS médiane = 7-26 mois
- **Toxicité ≥ G3 : < 6%**

	Patients (n)	Lesions (n)	Study design	Treated sites	Follow-up (months)	Dose and fractionation	Local control	Adverse events	
								Grade 3 (n)	Grade >3 (n)
Wersäll et al, <sup>41</sup> 2005	50	162	Retrospective	Lung, lymph node, kidney, adrenal, liver, spleen, bone, thoracic wall, pancreas	37	4 times 8–10 Gy; 2–3 times 15 Gy	90% (CR)	11	1
Svedman et al, <sup>48</sup> 2006	25	82	Prospective phase 2	Lung, lymph node, adrenal, thoracic wall, spleen	52	4 times 8–10 Gy; 2–3 times 15 Gy	79% (CR)	0	1 (?*)
Teh et al, <sup>46</sup> 2007	14	23	Retrospective	Bone, lung, lymph node, abdominal wall	9	24–40 Gy in 3–6 fractions	87% (CR)	0	0
Stinauer et al, <sup>7</sup> 2011	13	25	Retrospective	Lung, liver, bone	28	5 times 8–10 Gy; 3 times 14–20 Gy	88% at 1.5 yr	2	0
Zelevsky et al, <sup>16</sup> 2012	58	105	Retrospective	Bone, lymph node	12	Once 18–24 Gy; 3 times 8–10 Gy; 5 times 4–12 Gy; 24–37.5 Gy in more than five fractions	44% at 3.0 year	2	1
Ranck et al, <sup>9</sup> 2012	18	39	Retrospective	Bone, lymph node, lung, kidney, adrenal, liver, soft tissue	16	3 times 8–16 Gy; 10 times 4–5 Gy	91% at 2.0 yr	0	0

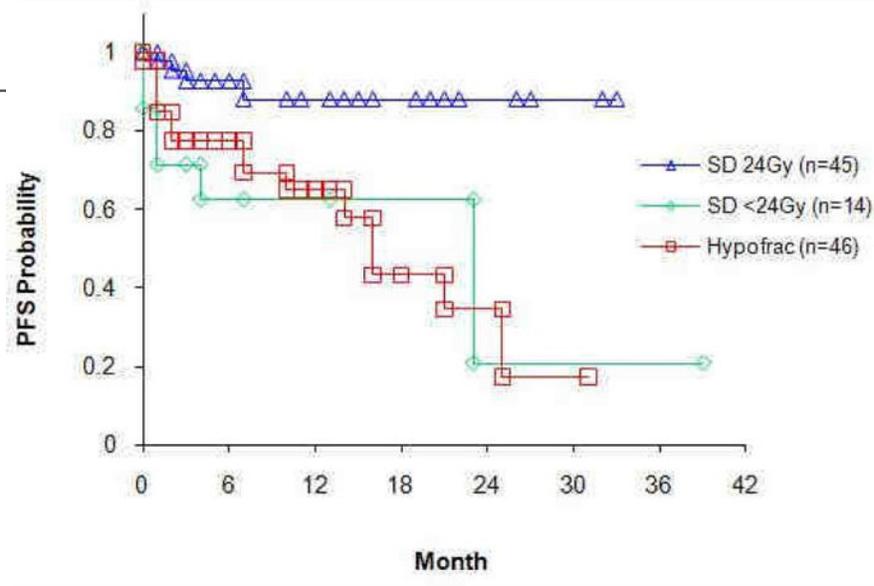
CR=crude rate. \*Stipulates the uncertainty that the one grade 5 toxicity was due to stereotactic body radiotherapy in this series.

**Table:** Studies of oligometastasis from renal-cell carcinoma with high-dose and high-dose-per-fraction radiotherapy

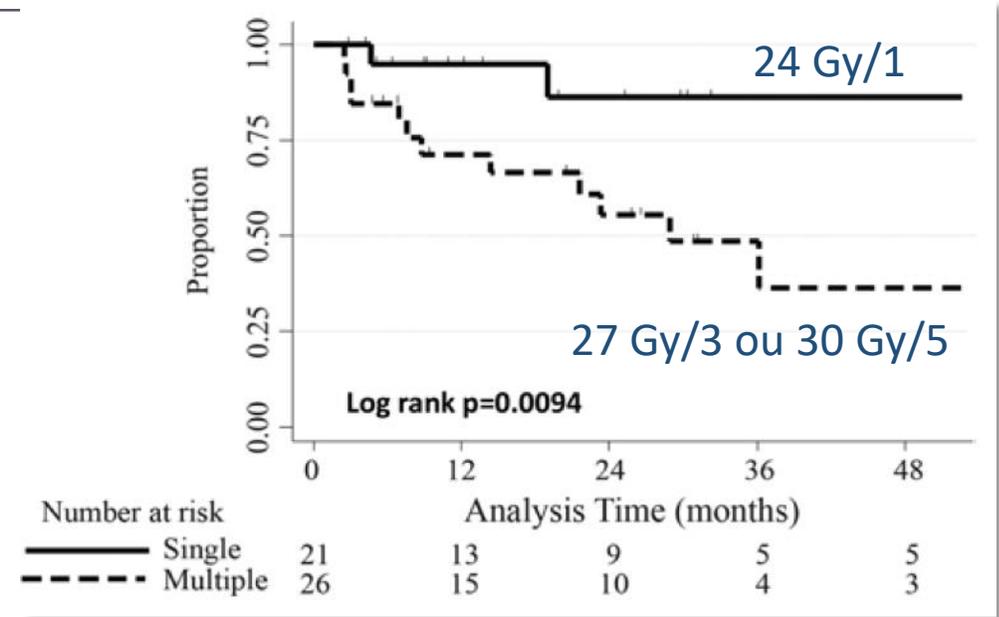
**LC proche  
de 80-90%**

**Tox G3-4 < 5%**

- Métas rachis + périphériques

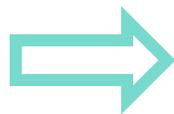


- Métas rachis



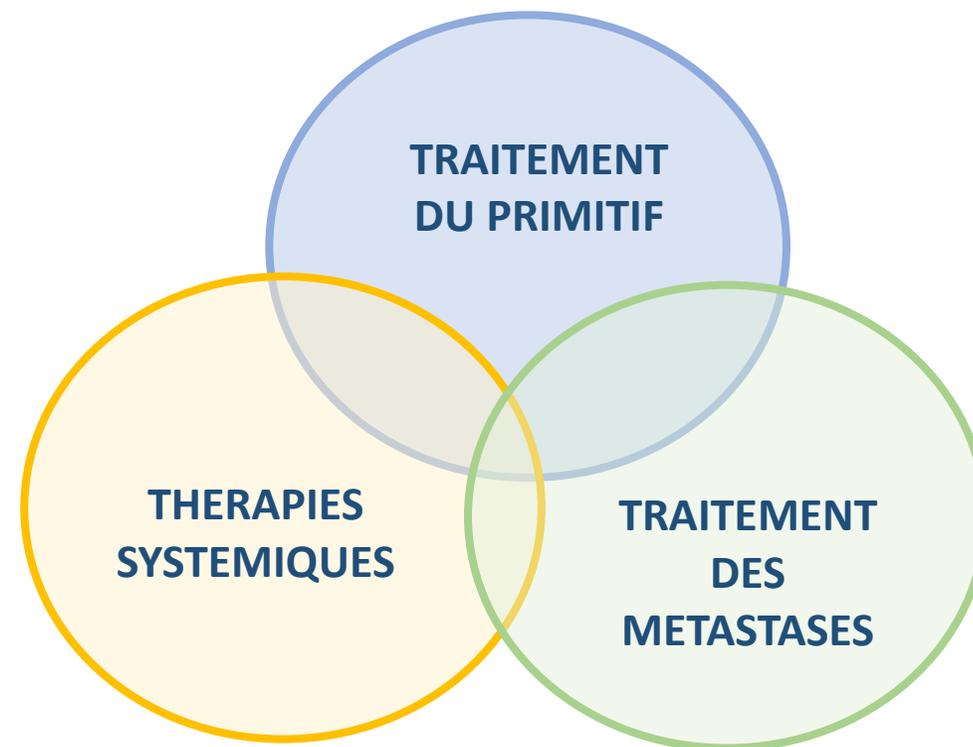
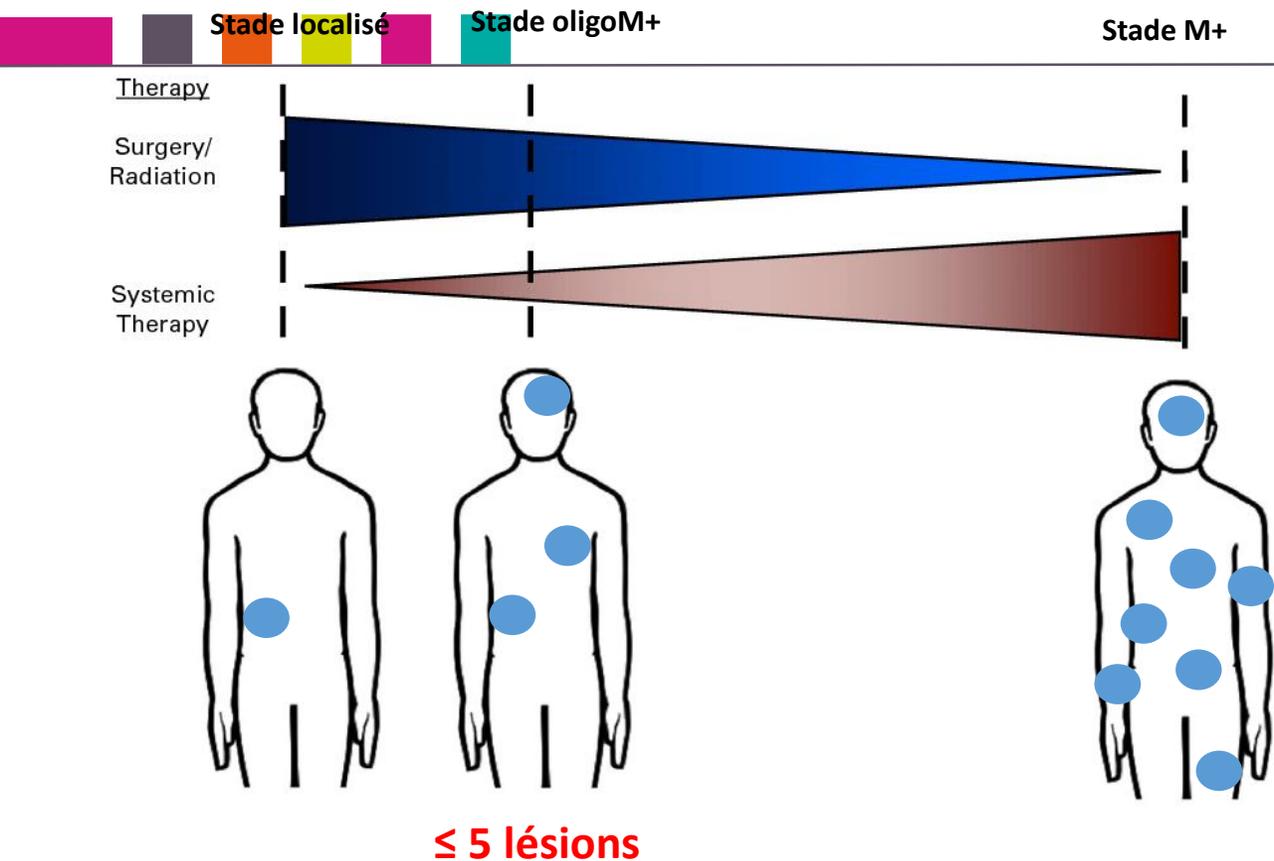
Cox Regression Analysis of Predictors of Local Progression Survival

Factor	Coefficient	95% Confidence (±)	Standard Error	P	Hazard Exp (Coefficient)
Single dose vs hypofractionation	-1.262	0.928	0.473	<u>0.008</u>	0.283
Volume PTV (cm <sup>3</sup> )	0.001	0.001	0.001	0.417	1.001
Dose ≥ 24 vs <24	-1.328	0.994	0.507	<u>0.009</u>	0.265



Association **DOSE** et **FRACTIONNEMENT** avec le **CONTROLE LOCAL**

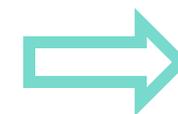
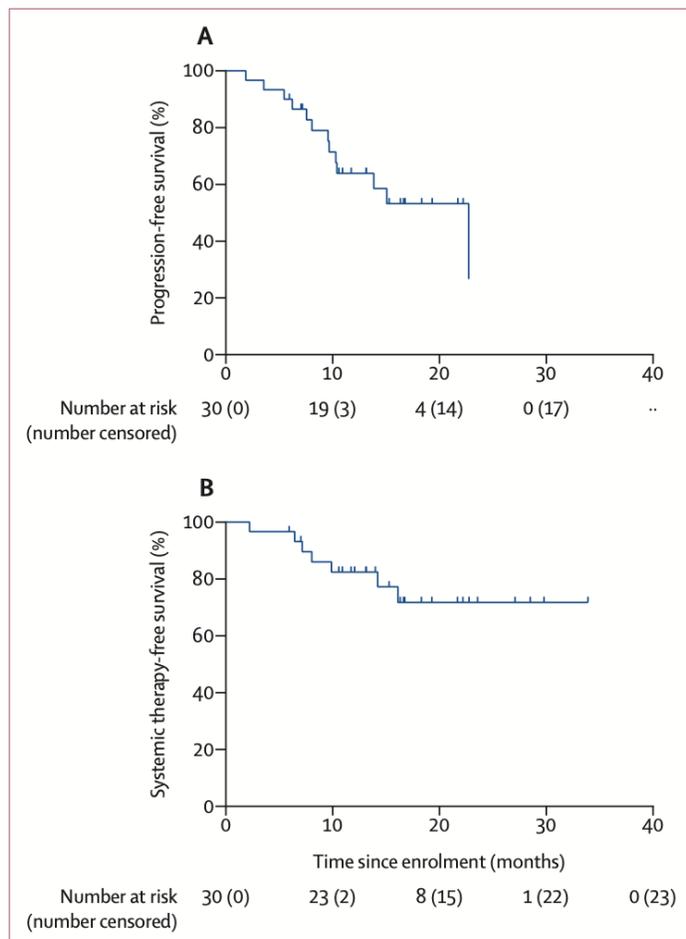
## INTENSIFICATION THERAPEUTIQUE



Definitive radiotherapy in lieu of systemic therapy for oligometastatic renal cell carcinoma: a single-arm, single-centre, feasibility, phase 2 trial

- Phase 2 de faisabilité
- Patients avec  $\leq 5$  lésions → SBRT de toutes les lésions
- $\leq 1$  ligne systémique

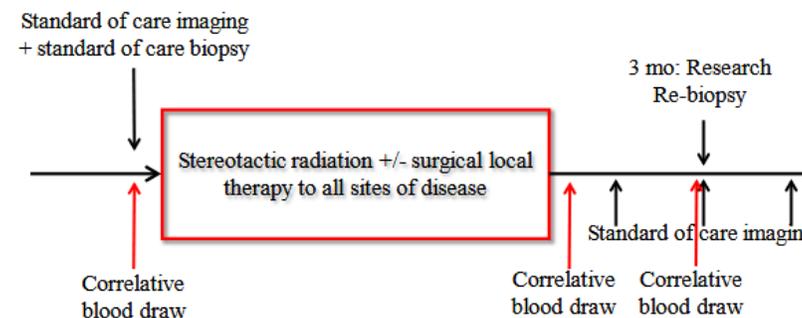
	First round of radiotherapy (n=30)	Second round of radiotherapy (n=13)
<b>Organ system involved (single or multiple lesions)*</b>		
Lung	20	6
Bone	6	2
Lymph node	4	3
Pancreas	3	0
Brain	1	1
Muscle	1	0
Liver	0	2
<b>Number of sites treated</b>		
1	20 (67%)	10 (77%)
2	8 (27%)	3 (23%)
3	1 (3%)	0
4	1 (3%)	0
<b>Radiation fractionation (dose per fractions)†</b>		
20–24 Gy per 1 per fraction	2	1
30–36 Gy per 3 fractions	5	3
54 Gy per 3 fractions	1	0
35–40 Gy per 5 fractions	3	0
50 Gy per 4 fractions	16	8
52.5 Gy per 15 fractions	5	3
60–67.5 Gy per 15 fractions	6	0
60–70 Gy per 10 fractions	7	1



PFS médiane 23 mois



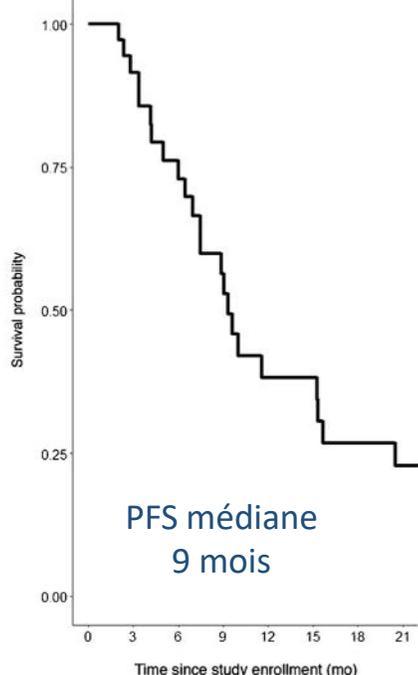
MDT diffère l'initiation des thérapies systémiques



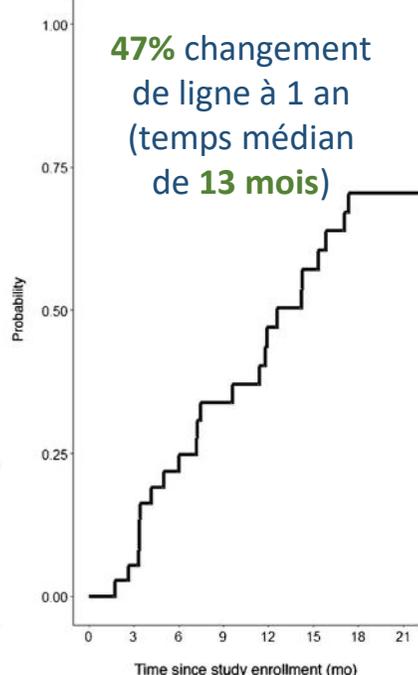
## Stereotactic Radiotherapy for Oligoprogression in Metastatic Renal Cell Cancer Patients Receiving Tyrosine Kinase Inhibitor Therapy: A Phase 2 Prospective Multicenter Study

- Patients M+ (synchrone ou métachrone)
- Stables ou répondeurs sous TKI ≥ 3 mois (sunitinib 95%/pazo 5%)
- Oligoprogessifs ≤ 5 lésions
- IMDC favorable ou intermédiaire

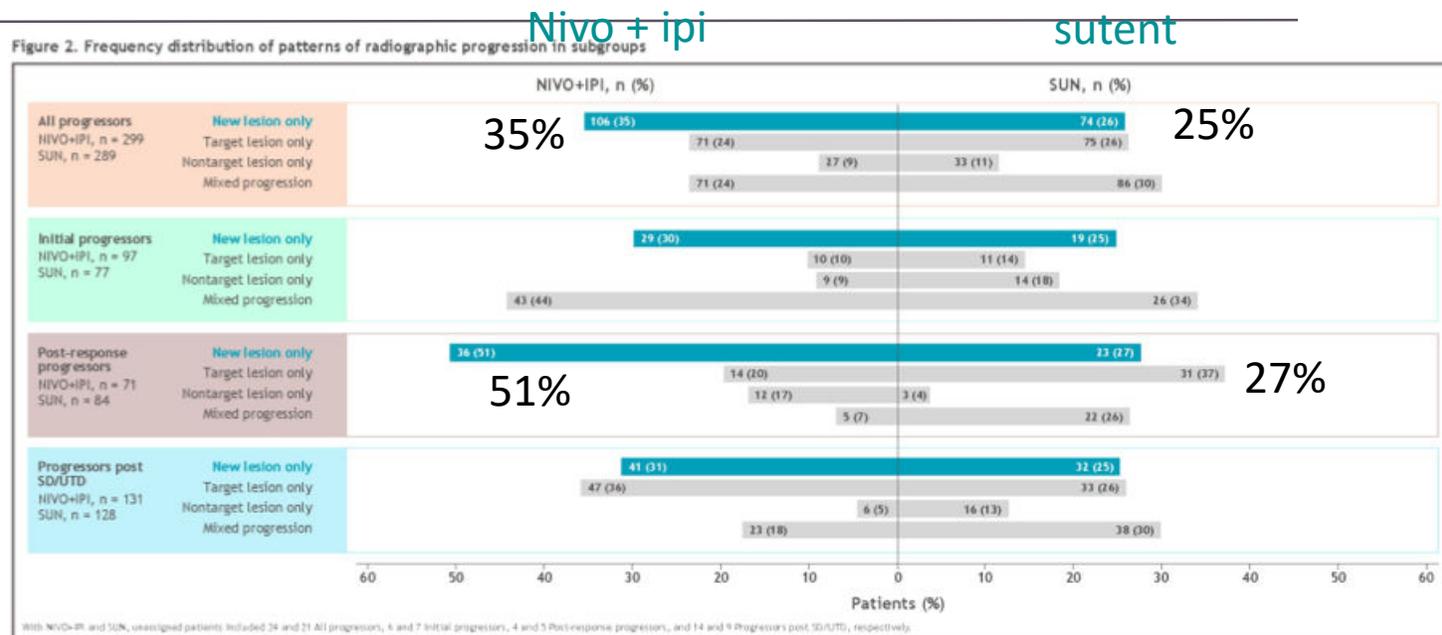
A. Progression-free survival



B. Cumulative incidence of changing systemic therapy



## PATTERN DE PROGRESSION à l'ère de IO



Davantage de récidive unisite après IO



**Place des thérapies focales en combinaison à IO : la question est ouverte !**

# Messages clés

- Une tumeur radiorésistante mais RADIOCURABLE avec ↑ dose par fraction
- Pas de place de la RT en (néo)-adjuvant en routine
- Un RATIONNEL radiobiologique et immunologique fort en faveur de la RT Stéréotaxique
- Littérature : contrôle local élevé en cas de stéréo du primitif, peu de toxicités... Mais niveau de preuve modéré
- Stéréotaxie des métastases (mRCC): une place assurée. Questions = timing et combinaison traitements
- Stéréotaxie du primitif (mRCC): faible niveau de preuve



Merci de votre attention  
@PBlanchardMD