# Comment l'imagerie nucléaire modifie-t-elle la prise en charge par radiothérapie des cancers de prostate ?

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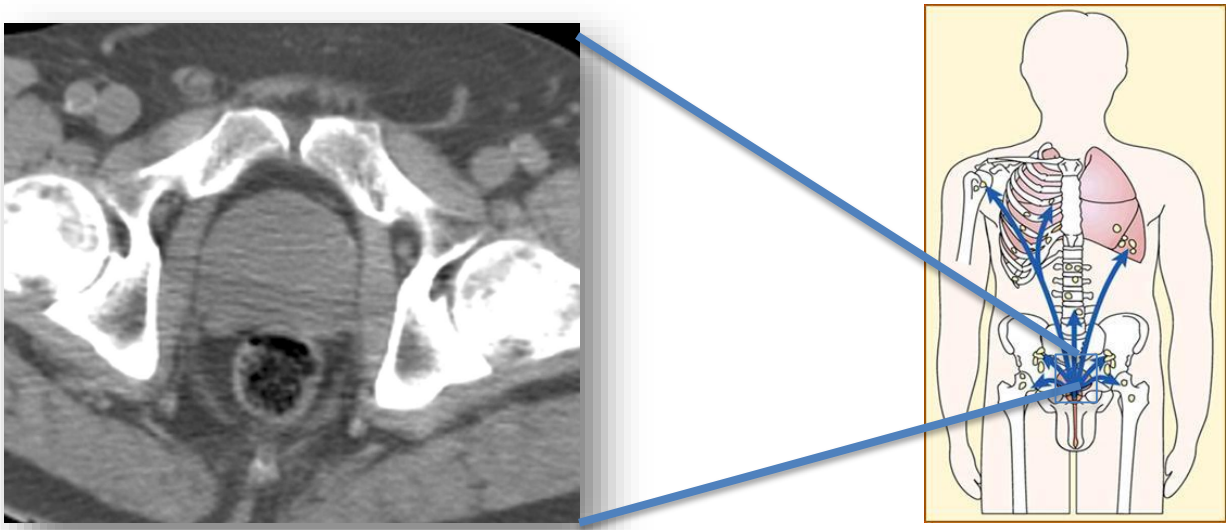
Centre de Recherche en Cancérologie Nantes Angers (CRCNA) U892 Inserm

UNIVERSITÉ DE NANTES

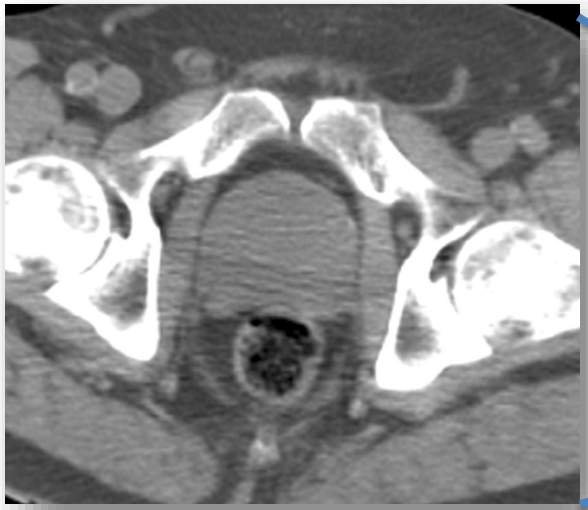
# Liens d’intérêts

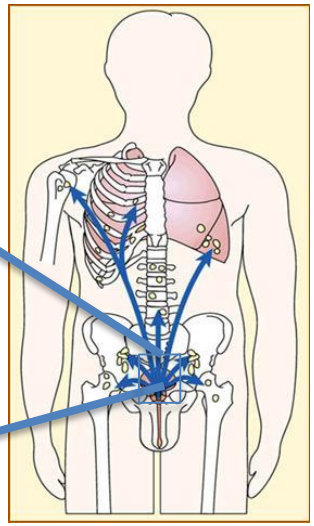
- Astra-Zeneca
- Ipsen
- Janssen
- Astellas
- Sanofi
- Novartis
- Takeda
- Ferring

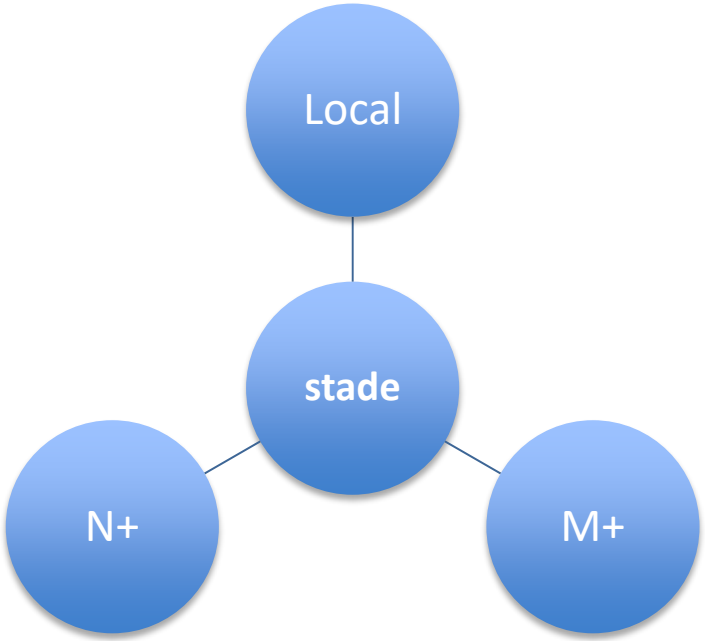


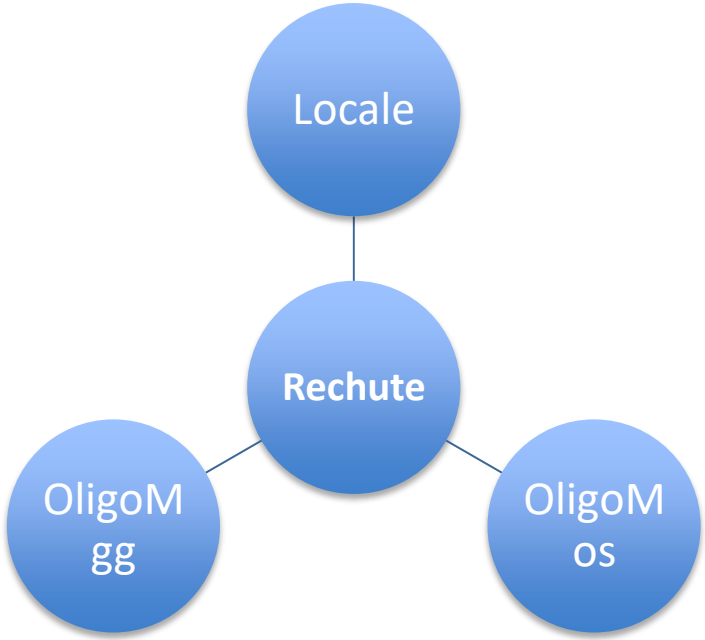
**Mieux définir le stade initial de la maladie**

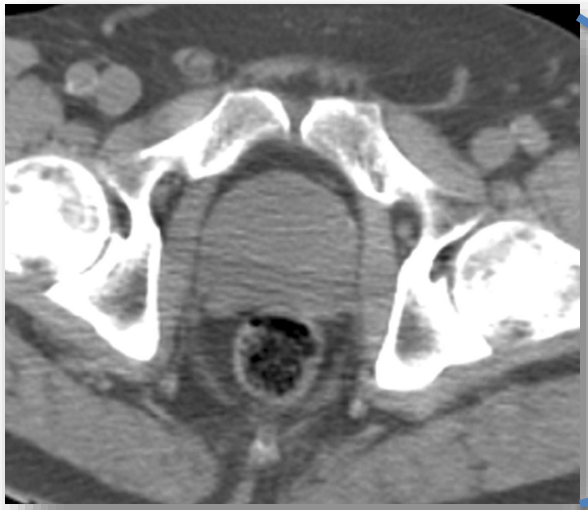
**Mieux définir le siège de la rechute**

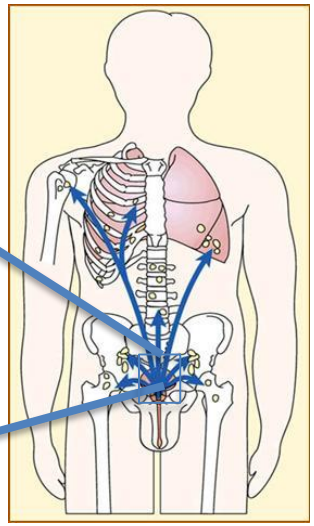


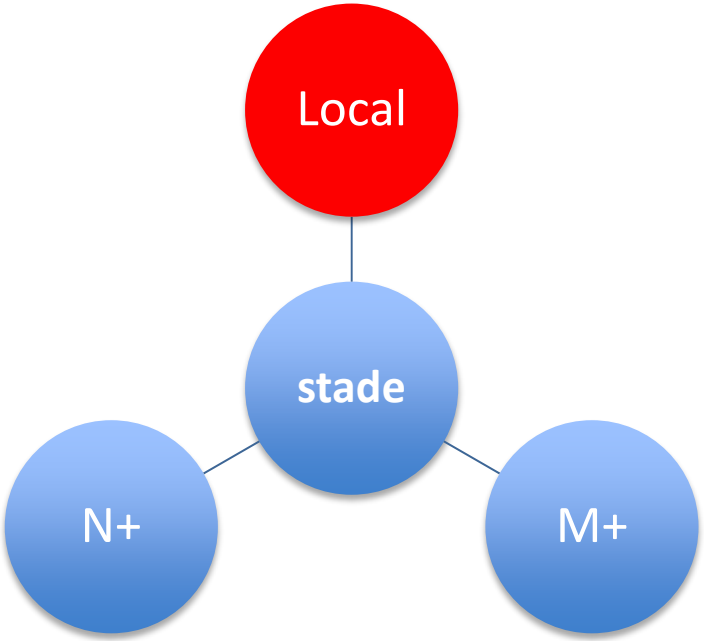


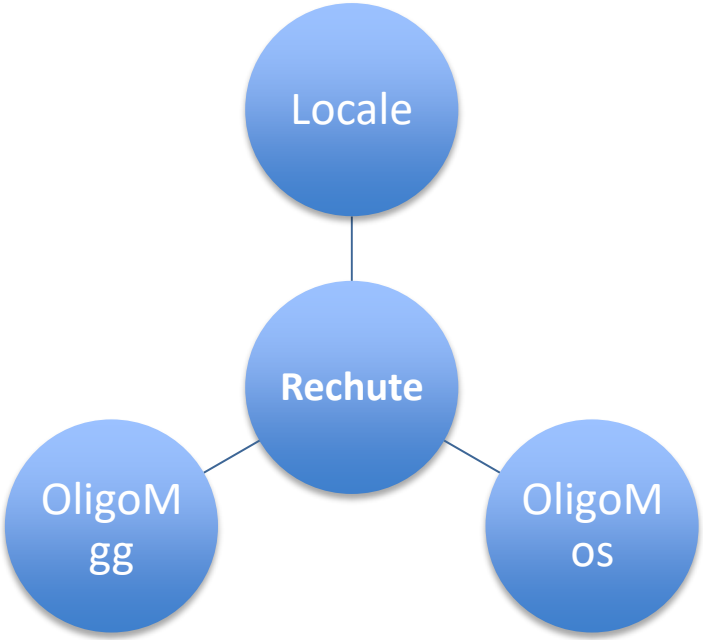

Local
stade
N+
M+


Locale
Rechute
OligoM gg
OligoM os



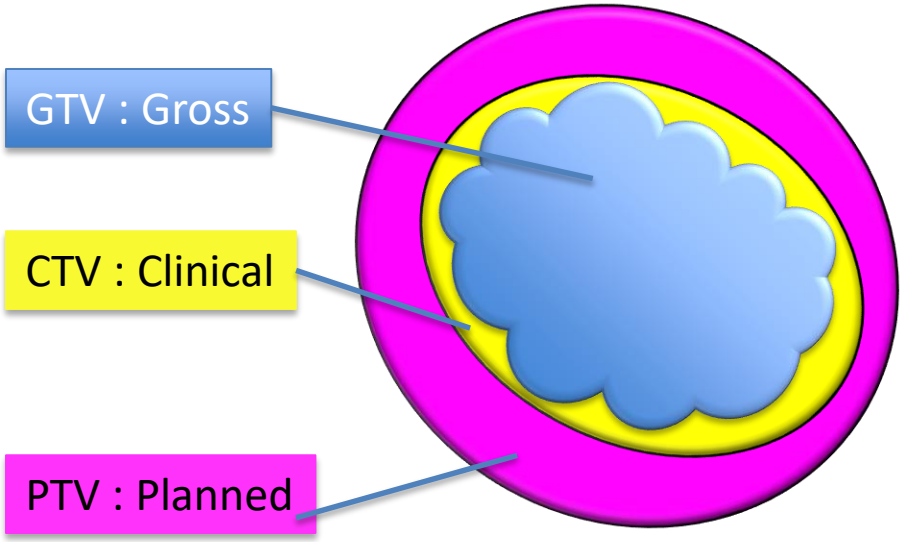



Local
stade
N+
M+

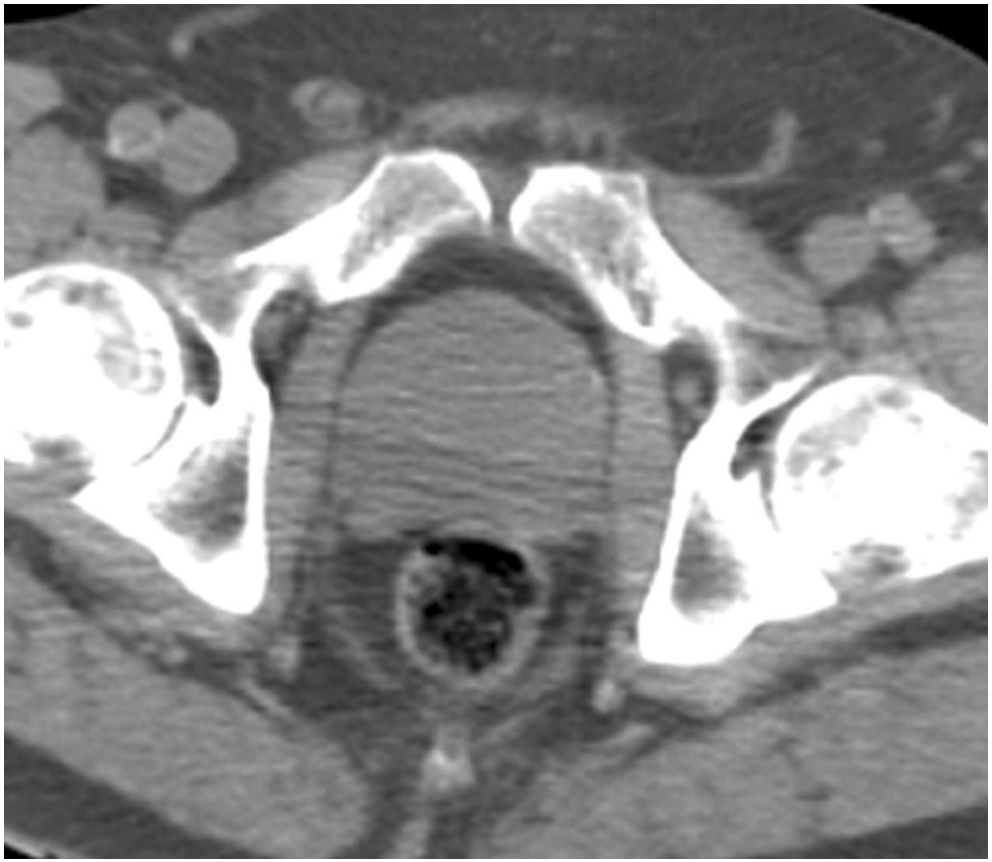

Locale
Rechute
OligoM gg
OligoM os

# Comment cibler la tumeur prostatique?

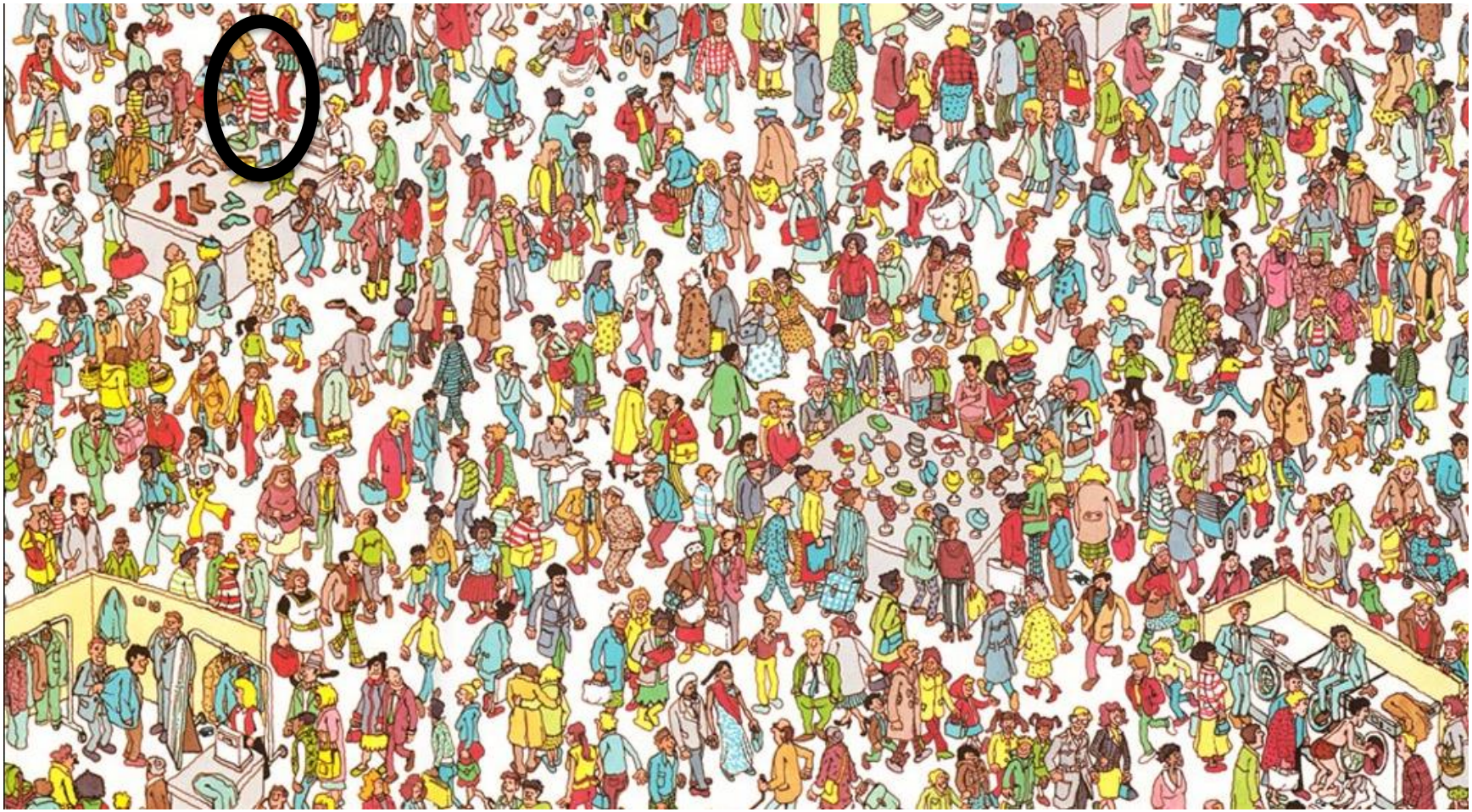
Différents volumes-cibles (Target Volumes)



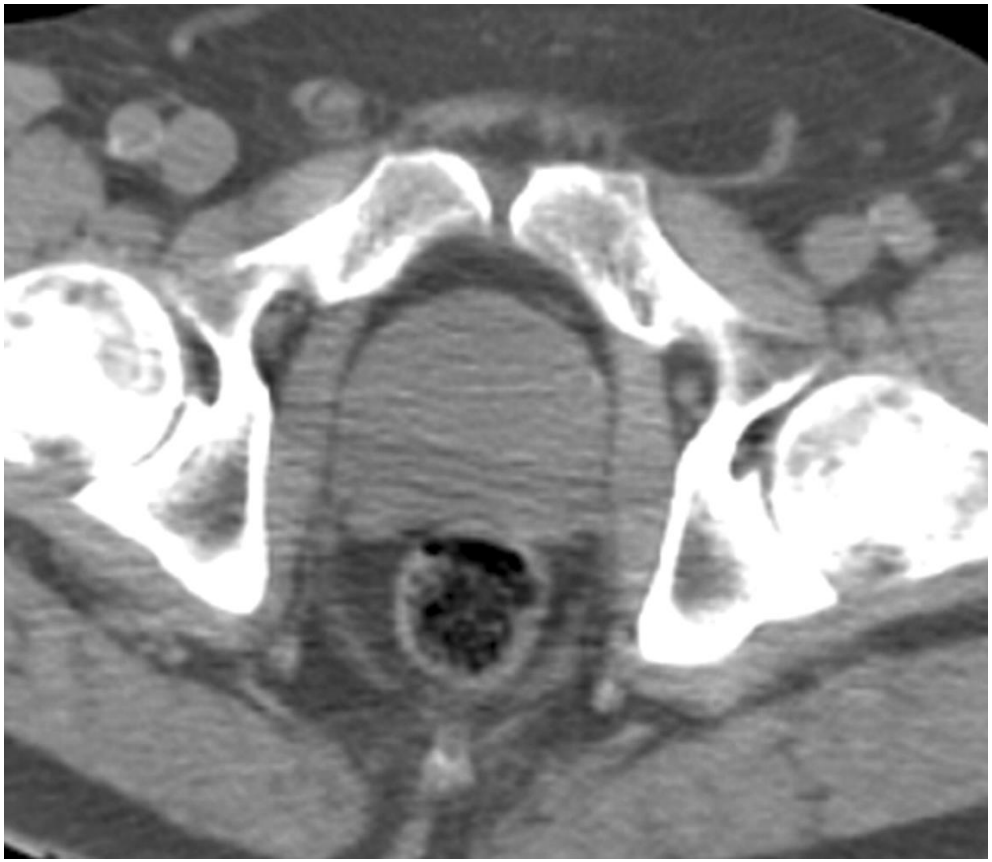
# Où est la tumeur ?



# Où est la tumeur ?



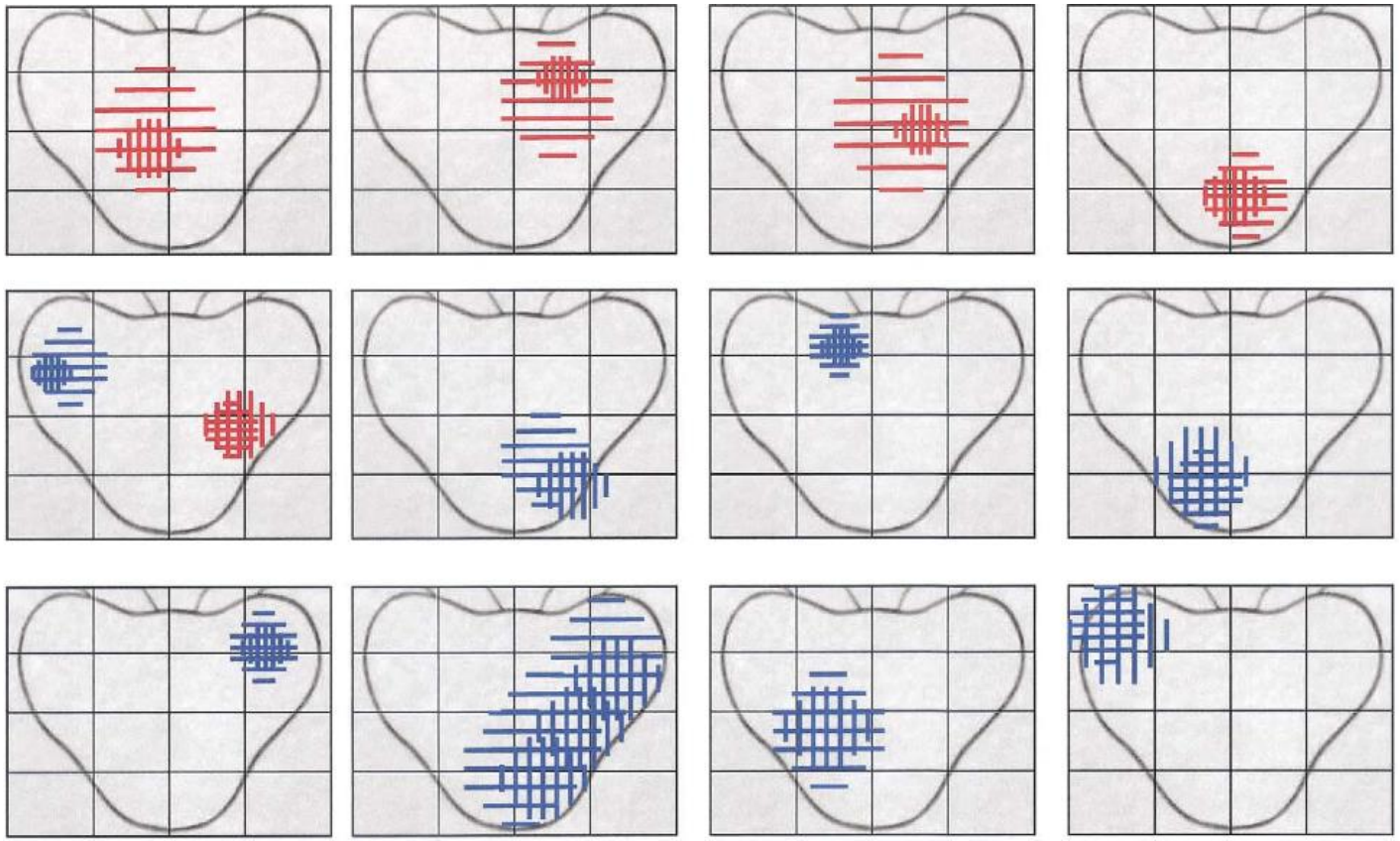
# Où est la tumeur ?



**Toute la prostate est traitée**

**CTV plutôt que GTV**

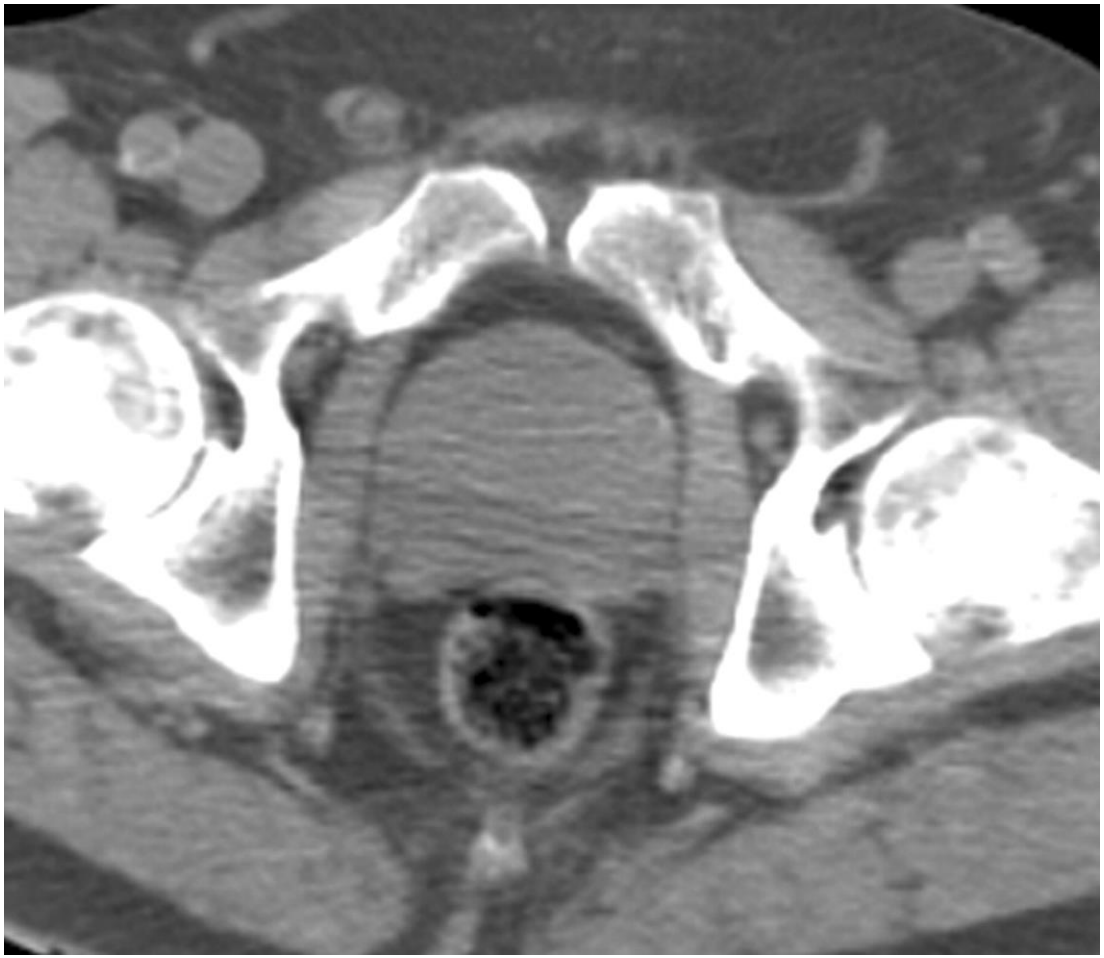
# Rechute locale après RT : dans le site tumoral initial



➔ Majorer dose de RT sur site tumoral intraprostatique?

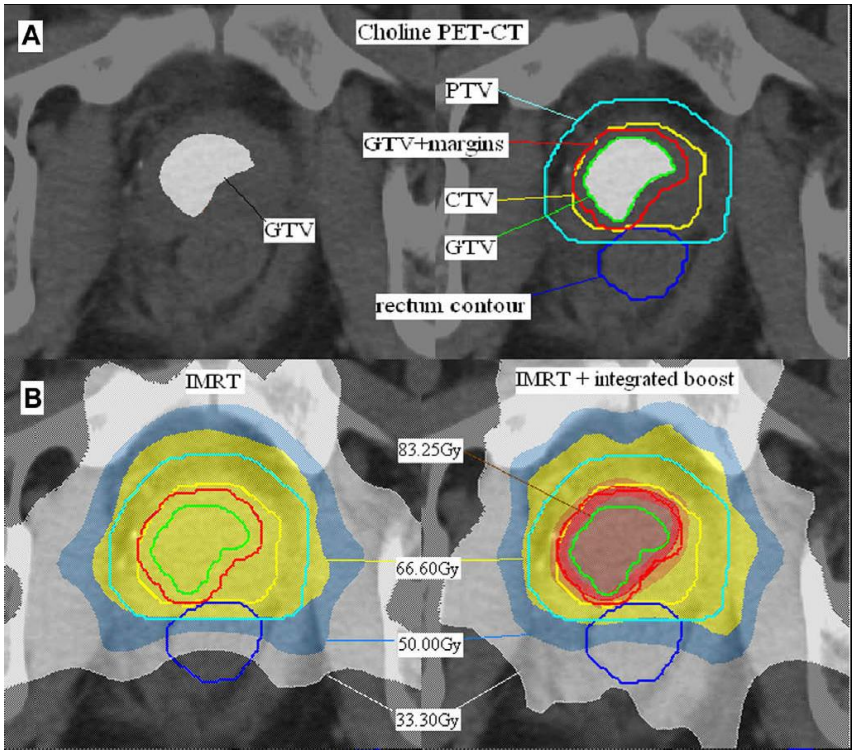
Cellini et al. Int J Radiat Oncol Biol Phys (2002) vol. 53 (3) pp. 595-9

# Comment définir un GTV (ou Dominant Intraprostatic Lesion - DIL) ?



- **IRM ?**
- **TEP ?**

# GTV $^{18}$F-Choline



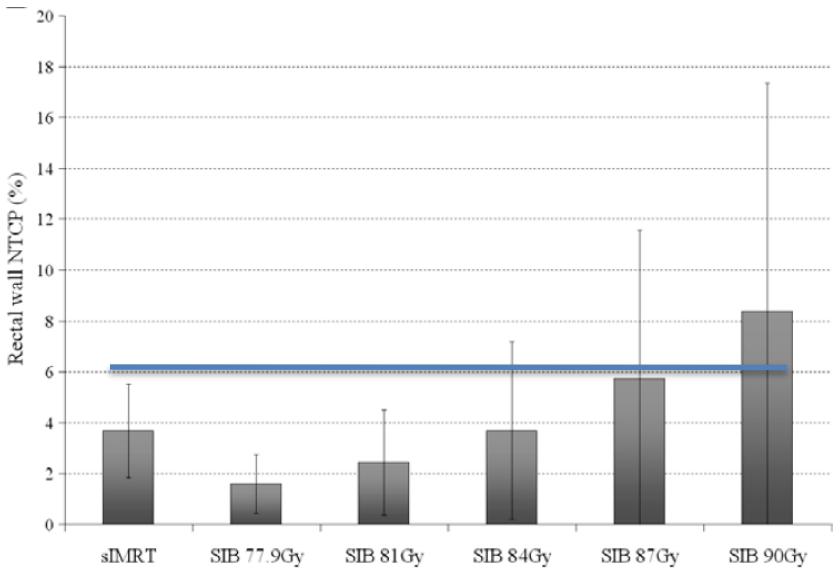

- Si PTV 66.6 Gy & BTV 83.25 Gy, pas d'augmentation de EUD à vessie ou rectum
- Si PTV 74 Gy & BTV 90 Gy, alors probabilité de contrôle tumoral (TCP) augmenté de 1,4 à 23.1

*Pinkawa et al; Radiotherapy and oncology (2009) vol. 93 (2) pp. 213-9*

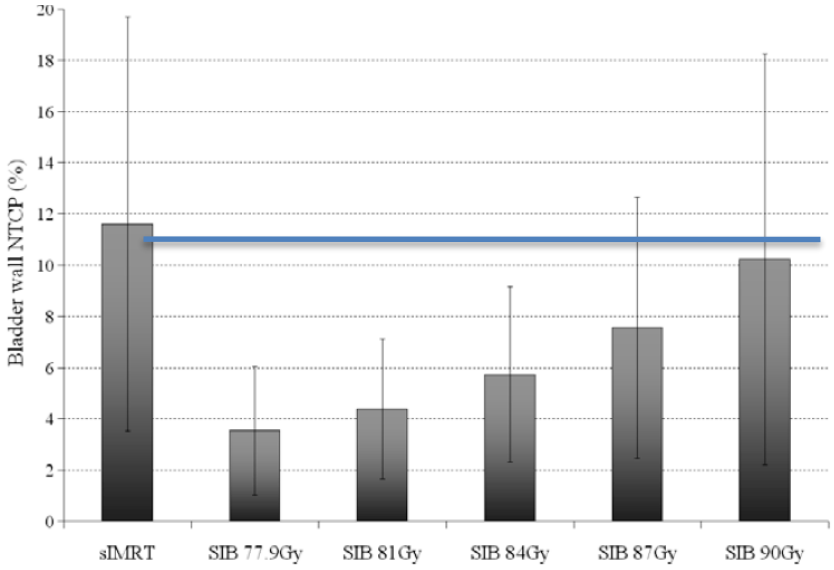
*Niyazi et al.; Radiat Oncol (2010) vol. 5 pp. 23*

# GTV $^{11}$C-acetate

## Vessie
## peu d'influence



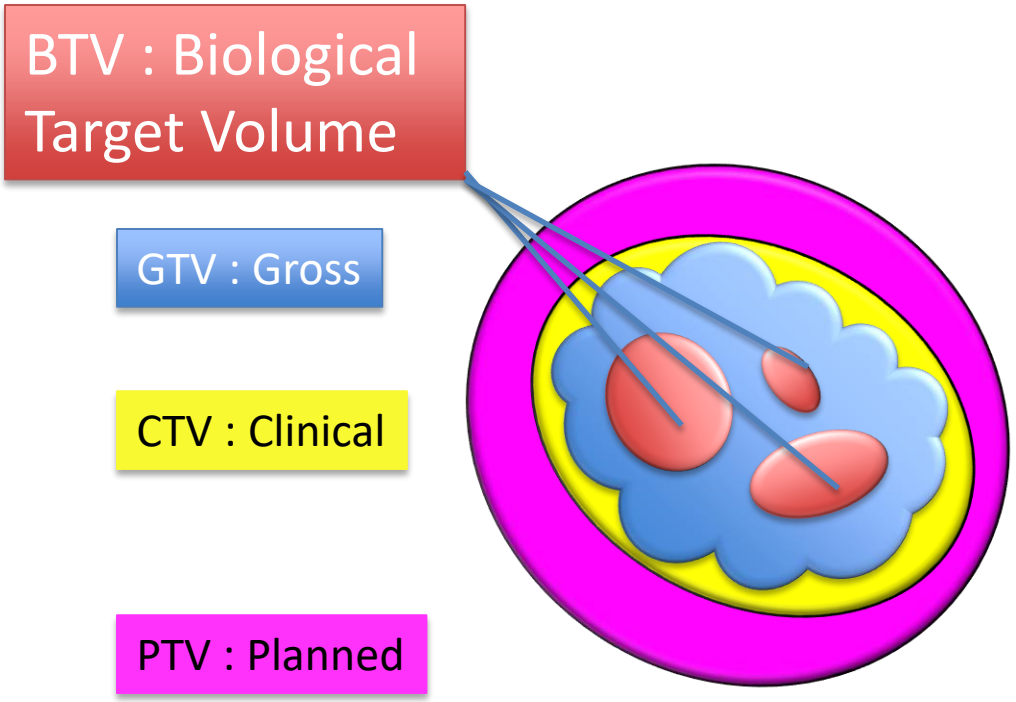

## Rectum
## EUD idem si 84 Gy



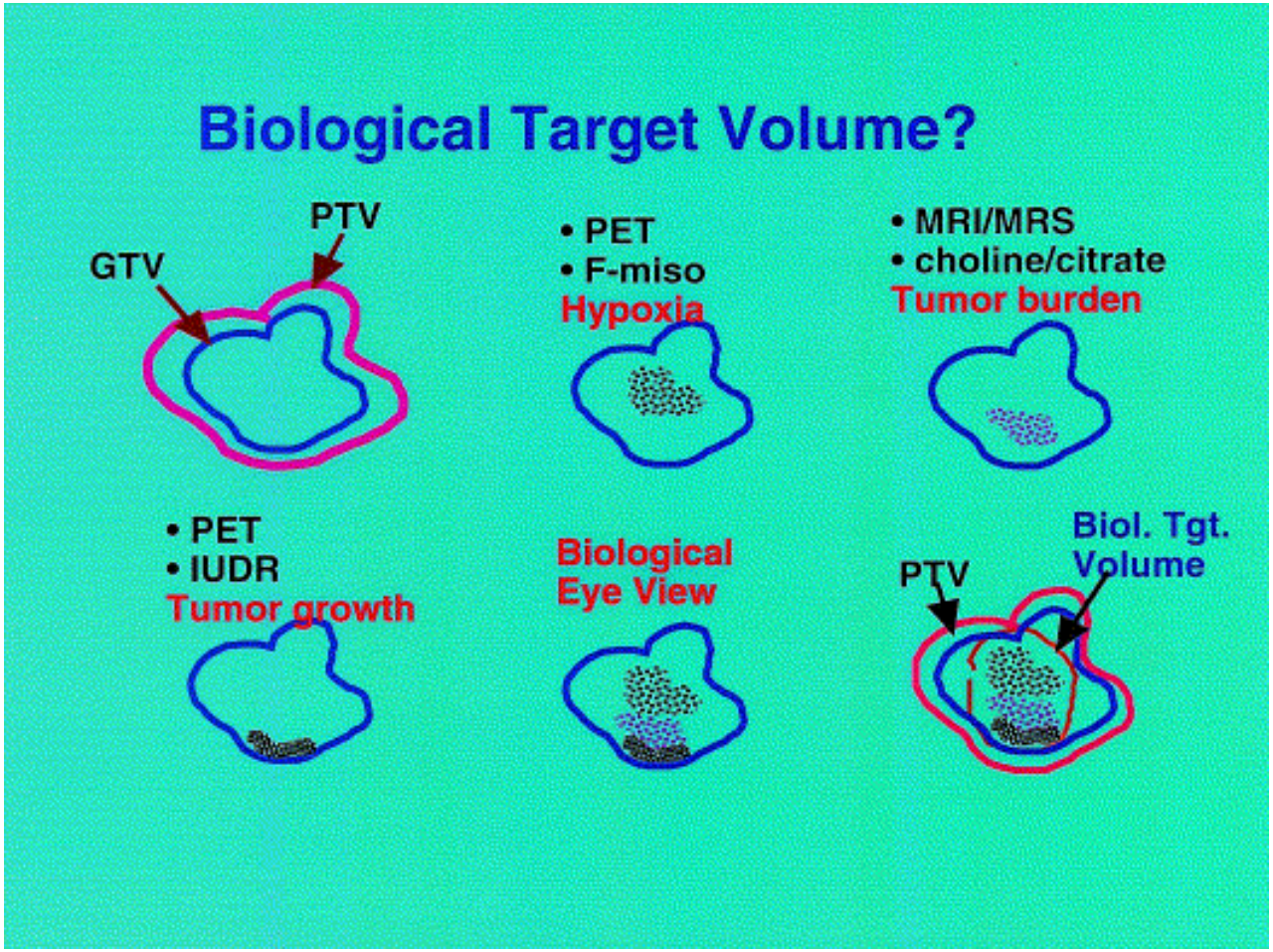

Pour 77,9 Gy PTV prostate

Seppälä et al. Radiother Oncol (2009) vol. 93 (2) pp. 234-40

# Renforcer la dose sur zones de radioresistance ?

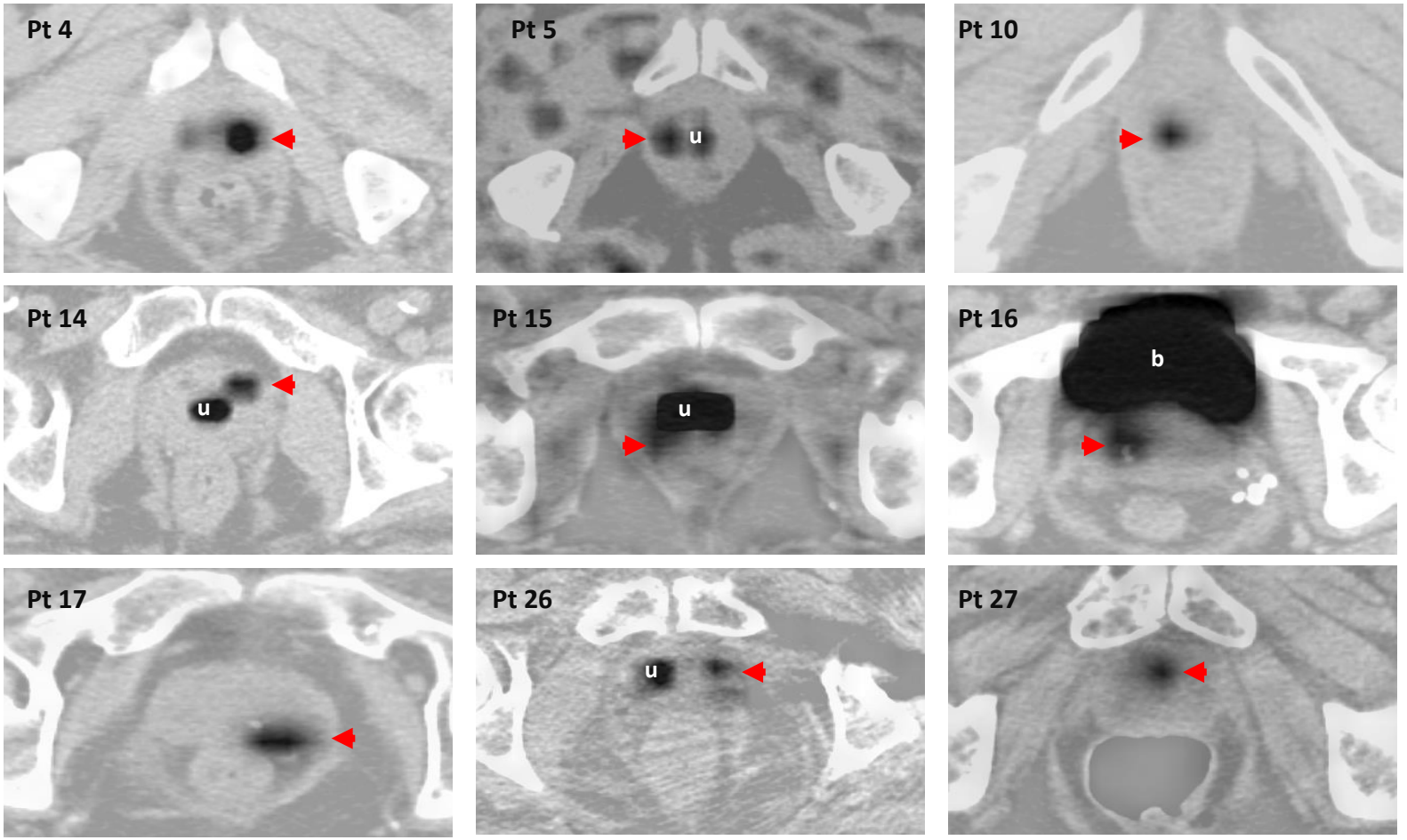


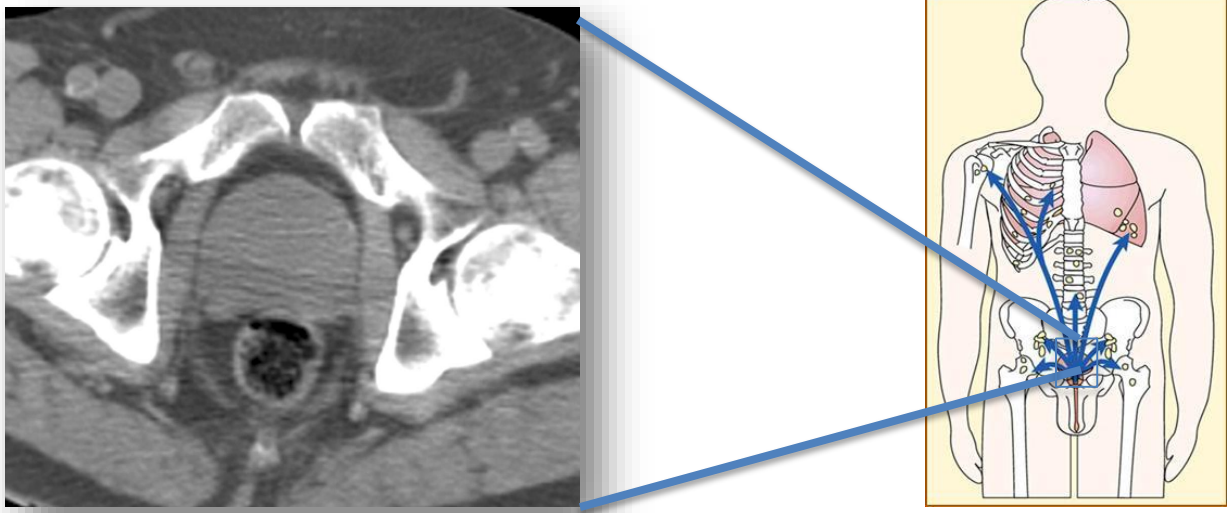
# « Peindre la dose » sur quel BTV ?

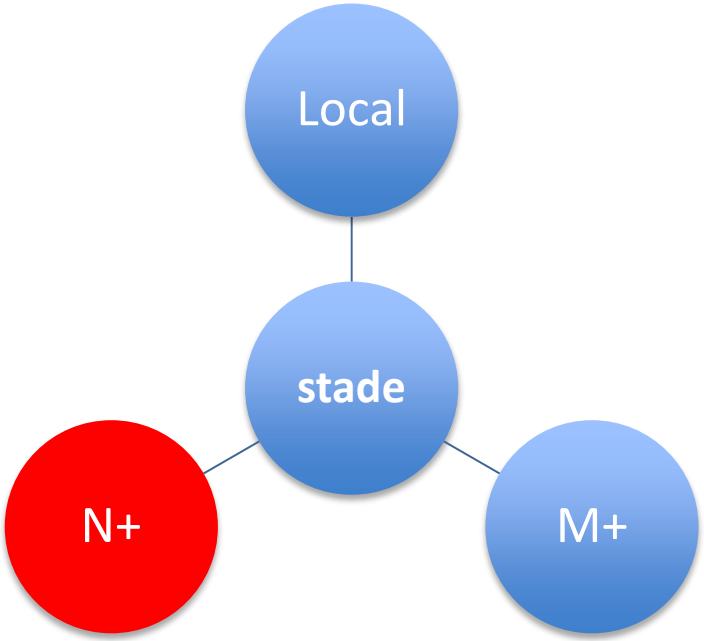


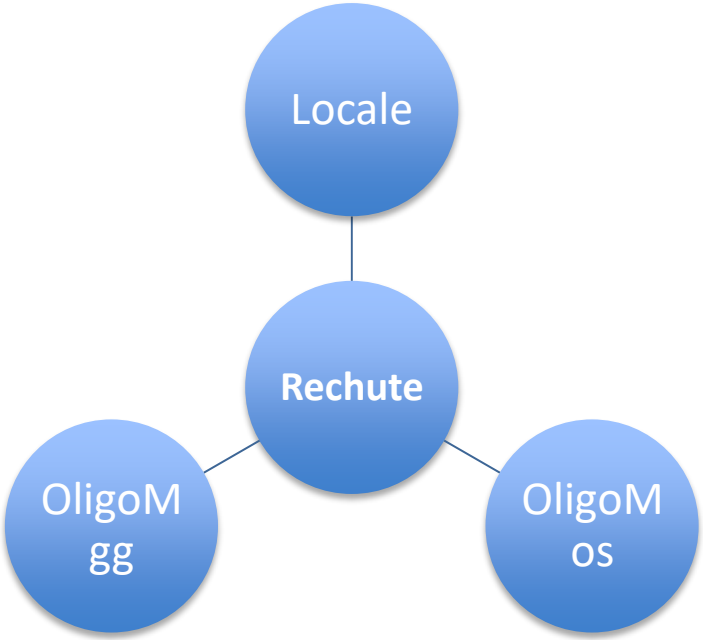

Ling *et al.*, *IJROBP 2000*

# BTV hypoxique ? TEP $^{18}$F-Misonidazole






Local
stade
N+
M+


Locale
Rechute
OligoM gg
OligoM os

**Patients cN1 :**
**pas de preuves de niveau 1 de l'utilité de la RT**

Néanmoins plusieurs preuves indirectes et études non randomisées

# Cancers de prostate de risque élevé: rôle indispensable RT HT

## RT+ HT > RT seule

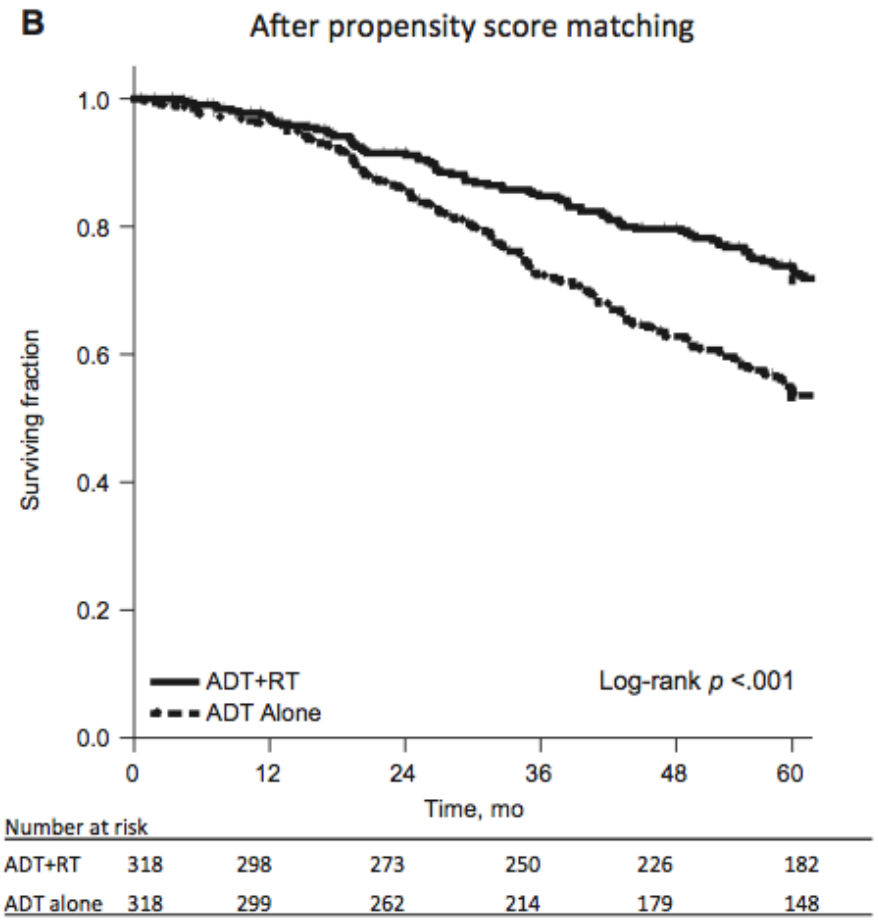
| | Protocole | SG (%) 8-10 ans |
|---|---|---|
| D'Amico, JAMA. 2008 | RT +/- HT 6 mois | 74 *vs* 61 s |
| Roach, JCO 2008 | RT +/- HT 4 mois | 43 *vs* 34 ns |
| Bolla, Lancet Onc 2010 | RT +/- HT 3 ans | 58 *vs* 39 s |

## HT +RT > HT seule

| Study | Protocole | OS (%) |
|---|---|---|
| Wildmark *et al.* (880 pts) | MAB (3 mo) + flutamide (cont)<br>RT 70 Gy | 29,6<br>39,4<br>*p = 0,004* |
| Warde *et al.* (1205 pts) | Orchidectomie ou ago LHRH (cont)<br>RT 65-69 Gy | 15<br>23<br>*p = 0,033* |
| Mottet *et al.* (273 pts) | Leuprorelin (3 ans)<br>RT 70 ± 4 Gy | 71,5<br>71,4<br>ns |

Martin, Supiot, Berthold. Pharmacotherapeutic management of locally advanced prostate cancer: current status. Drugs (2011)

# Données National Cancer Data Base (NCI)



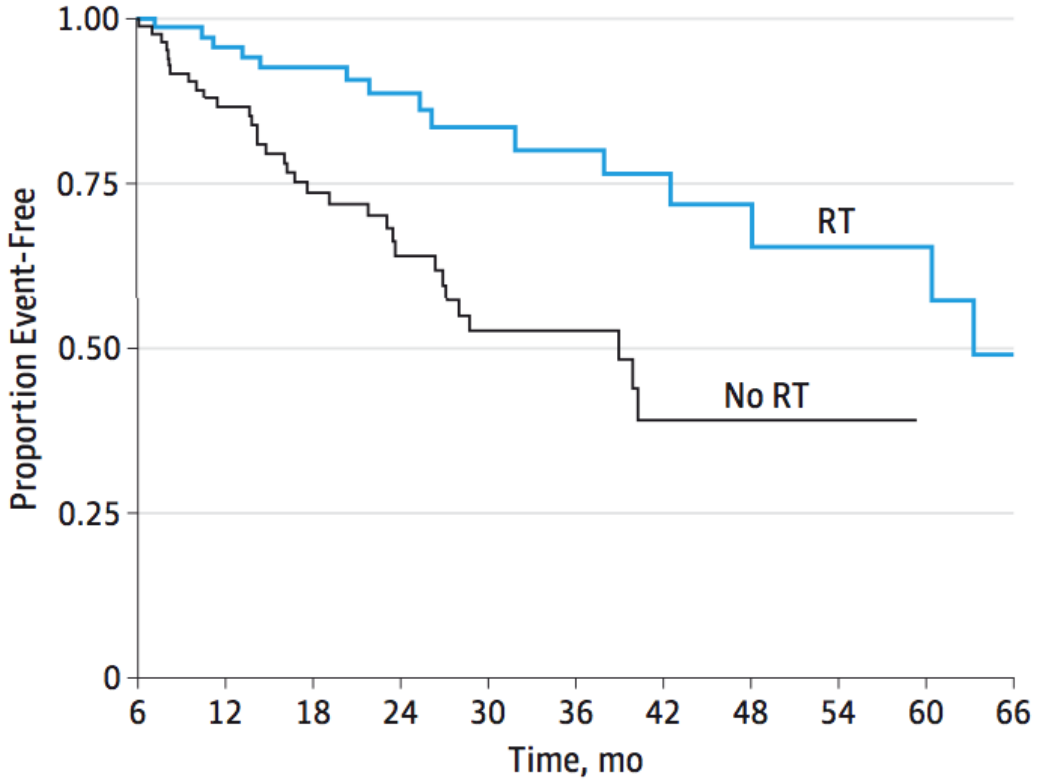

636 patients

survie à 5 ans dans le groupe irradié (72% contre 53%, p<0,001)

**RT = +20 % à 5 ans**

Lin et al. Androgen deprivation with or without radiation therapy for clinically node-positive prostate cancer. JNCI (2015) vol. 107 (7)

# Données prospective STAMPEDE




No. at risk (events)

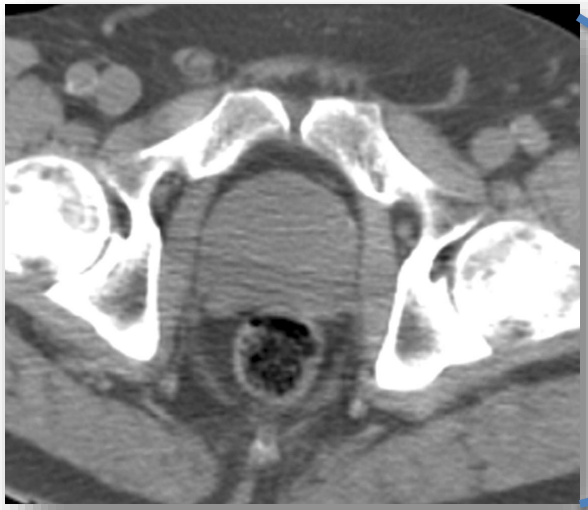
| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No RT | 86 | (20) | 47 | (10) | 20 | (3) | 8 | (0) | 6 | (0) | 3 |
| RT | 71 | (5) | 54 | (4) | 28 | (2) | 17 | (2) | 9 | (2) | 6 |

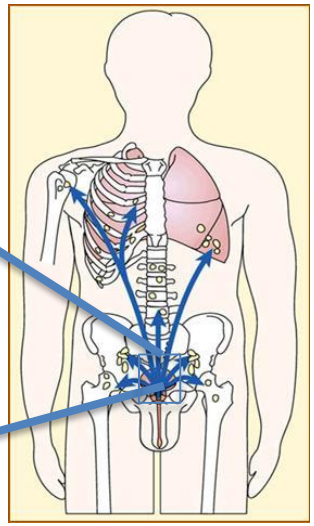
177 pts
Prostate 74 Gy in 37 f
Pelvis optionnel :46 -50 Gy 2 Gy/f
ou SIB 55 Gy, 37 f

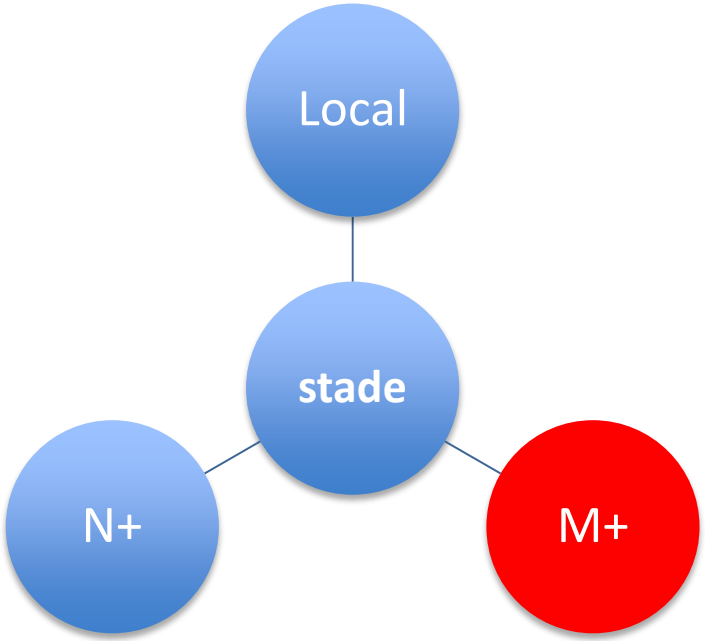
82% (58 of 71) prostate + pelvis,

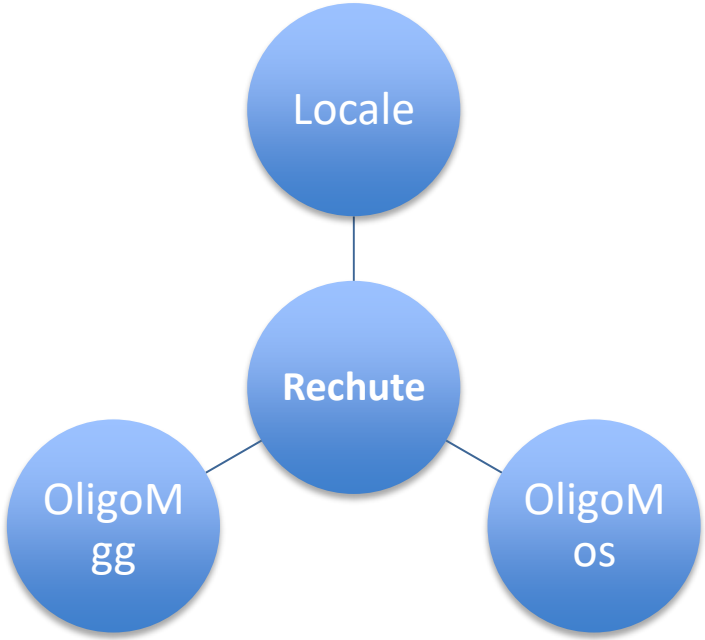
Tolérance : Pas de tox dig G3

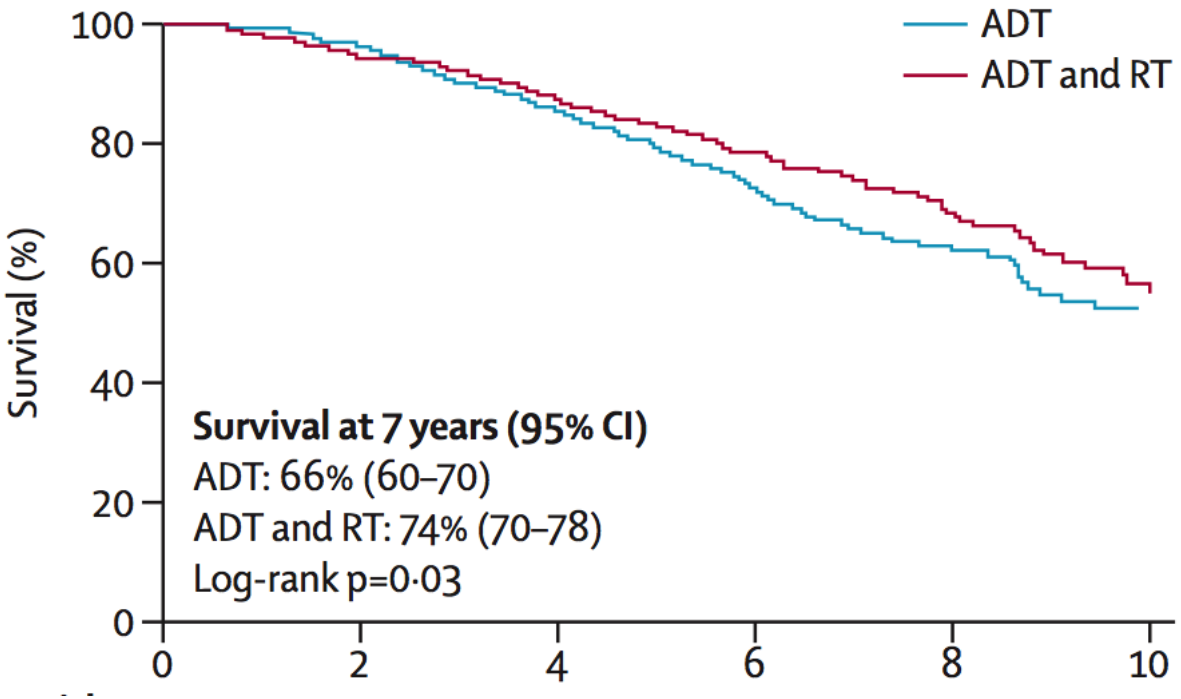
James et al. Failure-Free Survival and Radiotherapy in Patients With Newly Diagnosed Nonmetastatic Prostate Cancer: Data From Patients in the Control Arm of the STAMPEDE Trial. JAMA Oncol (2015) pp. 1-10






Local
stade
N+
M+


Locale
Rechute
OligoM gg
OligoM os

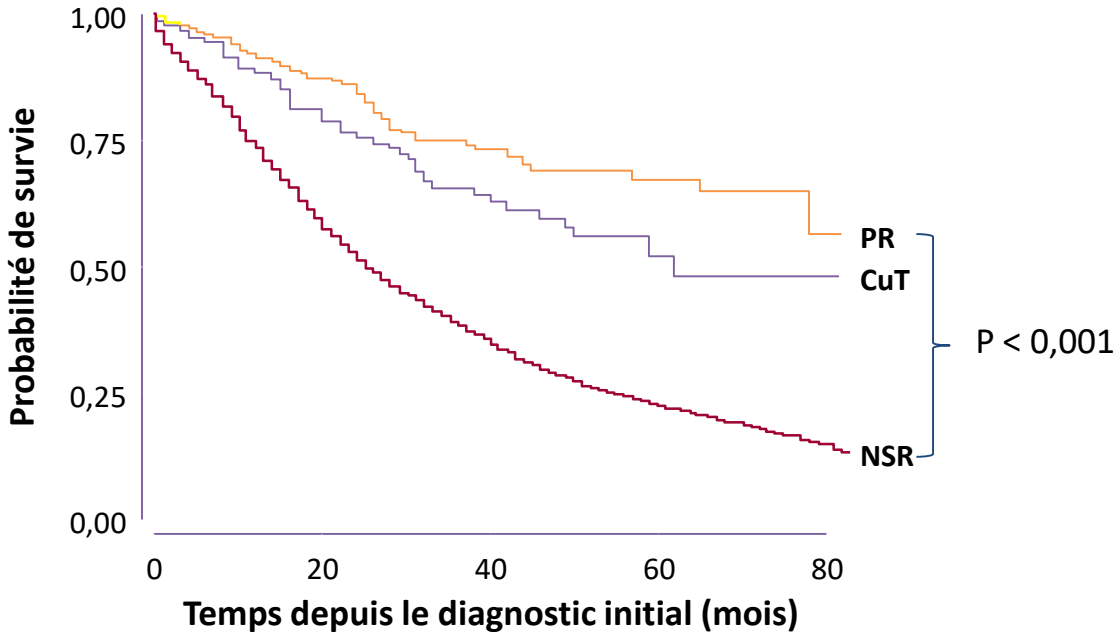



**K prostate de haut risque = Maladie micrométastatique d'emblée ?**

**OR : études faites à époque où imagerie moins précise = Rôle RT si métastases d'emblée ?**

Morgan et Parker. Local treatment of metastatic cancer--killing the seed or disturbing the soil?. Nature Reviews Clinical Oncology (2011)

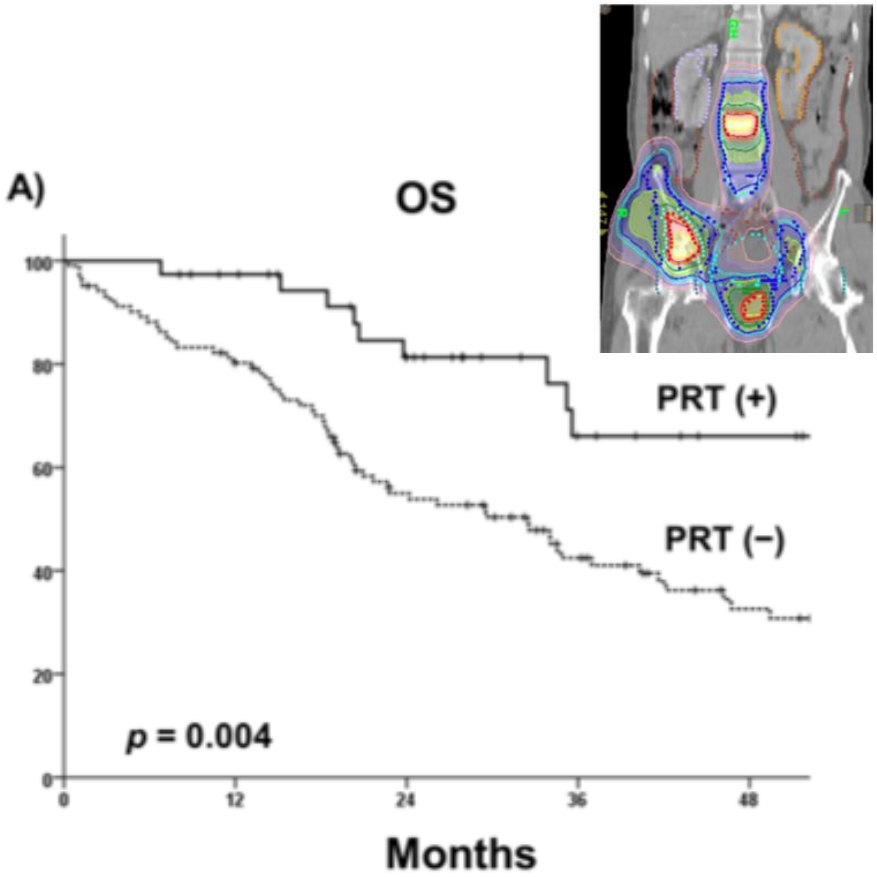
# Survie globale selon le traitement reçu : ttt tumeur primitive améliore la survie ?

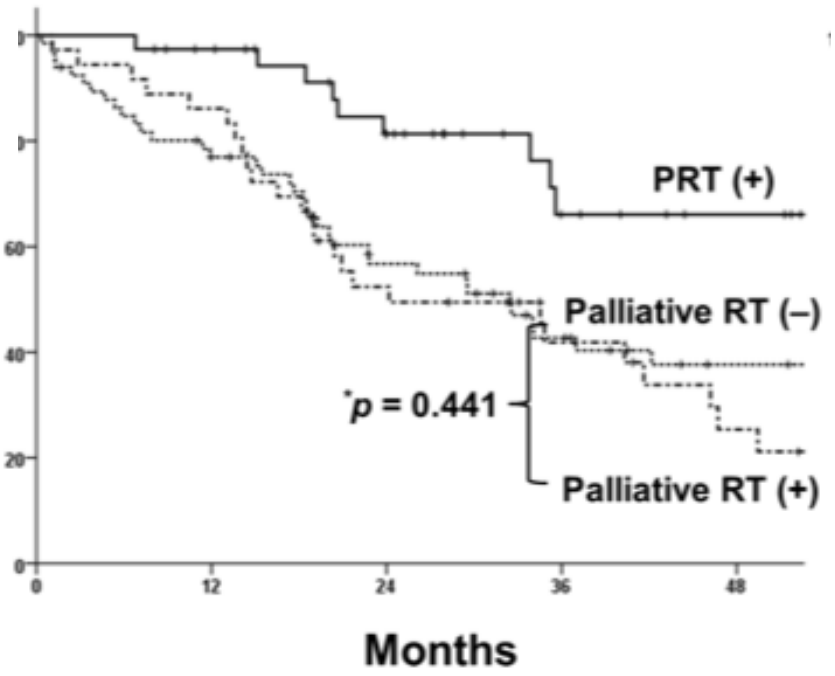



**PR** Prostatectomie (245 pts)
**CuT** Curiethérapie (129)
**NSR** Pas de chirurgie ni irradiation (7811)

Culp et al. Might Men Diagnosed with Metastatic Prostate Cancer Benefit from Definitive Treatment of the Primary Tumor? A SEER-Based Study. European Urology (2014)

# Faut-il irradier la prostate si patient M+ ?




Cho et al. Does Radiotherapy for the Primary Tumor Benefit Prostate Cancer Patients with Distant Metastasis at Initial Diagnosis?. PLoS ONE (2016) vol. 11 (1) pp. e0147191

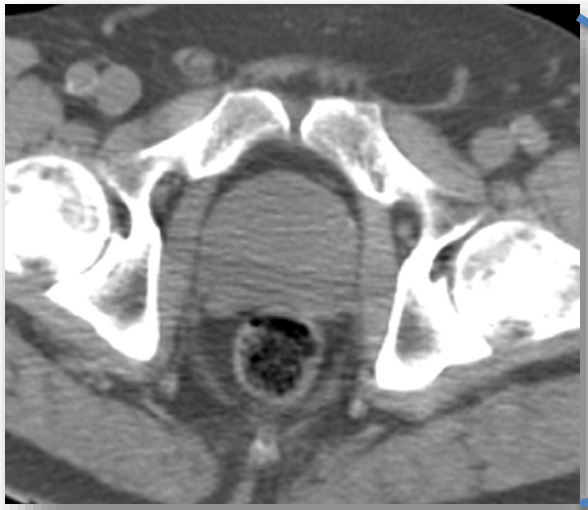
# PEACE 1 – GETUG 21 : K prostate M+ d'emblée

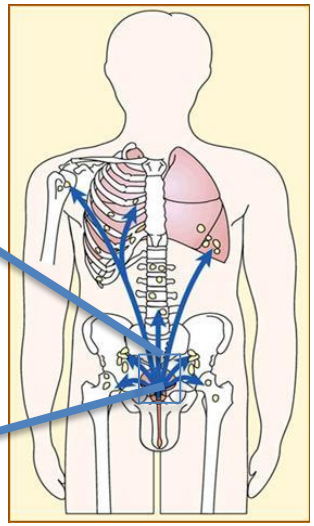
1. Adenocarcinome de prostate
2. Métastases osseuses
3. **Ou** Métastases ou ganglionnaires si
   - Au moins un gg extra-pelvien >2 cm
   - Un ganglion extra-pelvien >1 cm si ganglion pelvien >2 cm

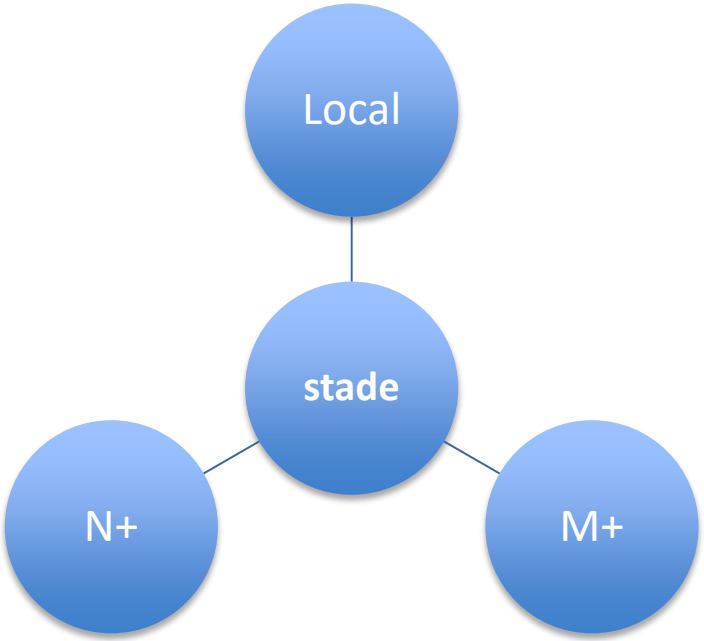
**RANDOMISATION**

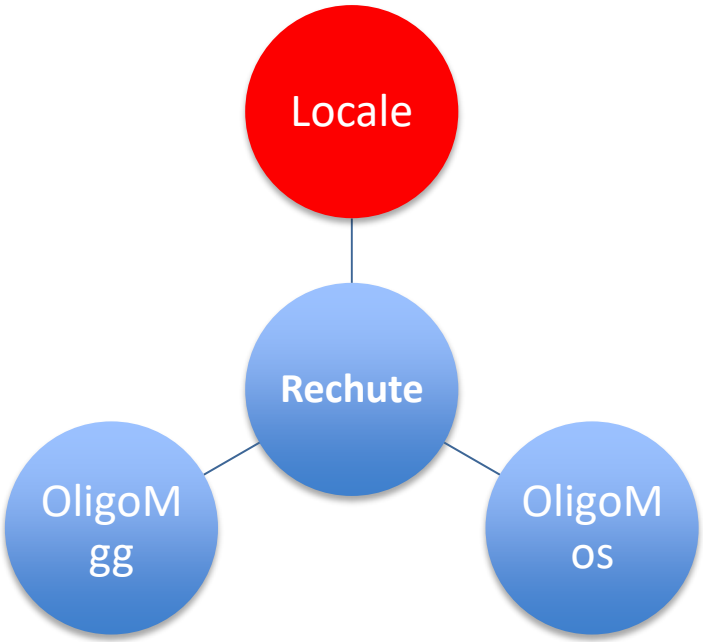
| Bras A | Bras B | Bras C | Bras D |
|---|---|---|---|
| Thérapie anti-androgénique | Thérapie anti-androgénique + Abiratérone 1000 mg/j et prednisone 5 mg 2x/j | Thérapie anti-androgénique + Radiothérapie | Thérapie anti-androgénique + Abiratérone 1000 mg/j et prednisone 5 mg 2x/j + Radiothérapie 74 Gy |

**La radiothérapie doit débuter dans les 8 semaines après la randomisation**





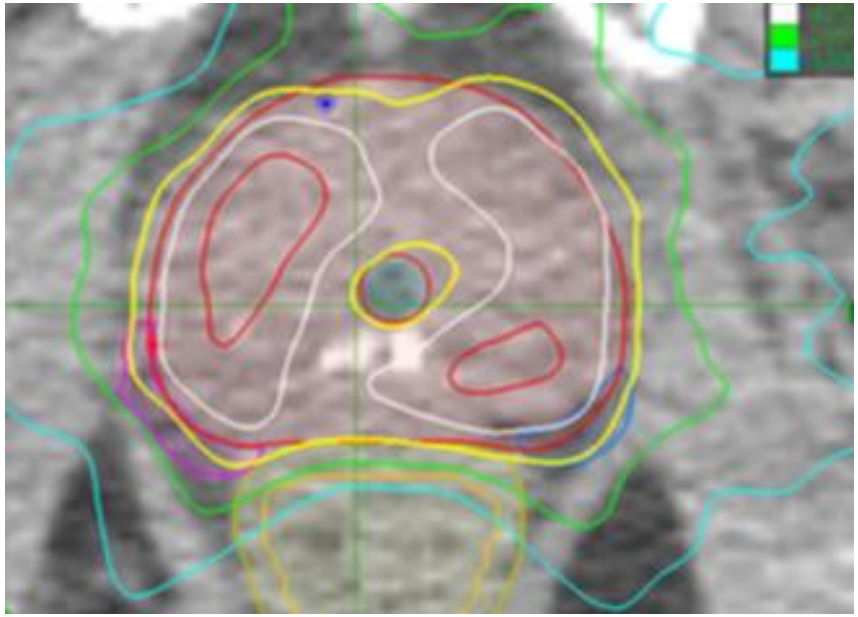

Local
stade
N+
M+


Locale
Rechute
OligoM gg
OligoM os

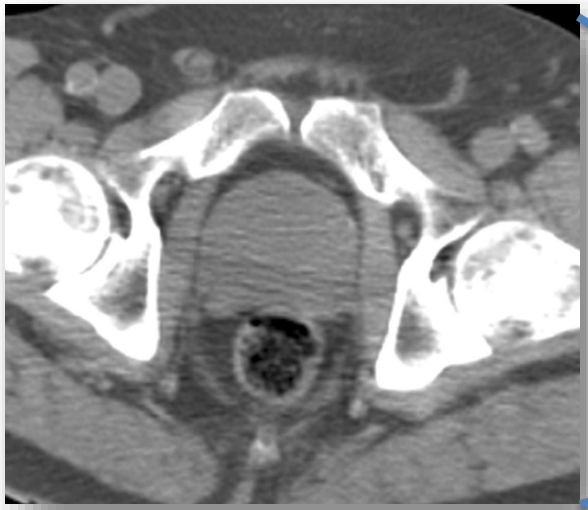
# Prendre en charge la rechute locale après RT

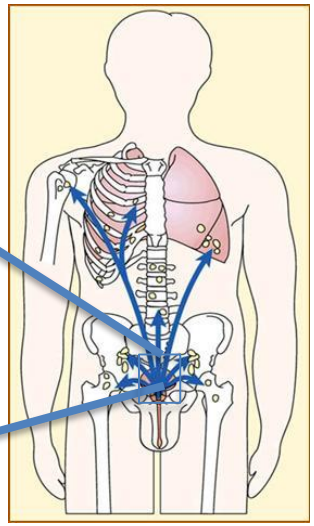
- Chirurgie
- HIFU
- Cryo
- Curie
- RT Stéréo

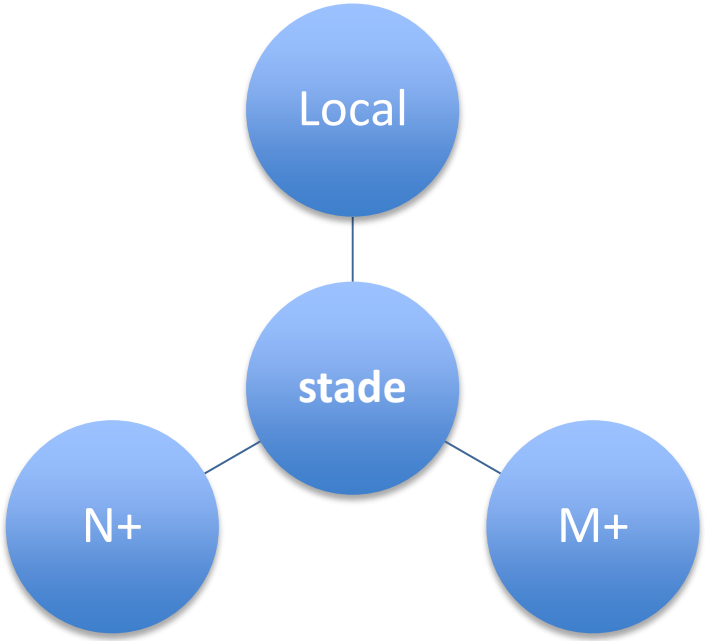
GETUG 31 STEREO-RE-PRO_01

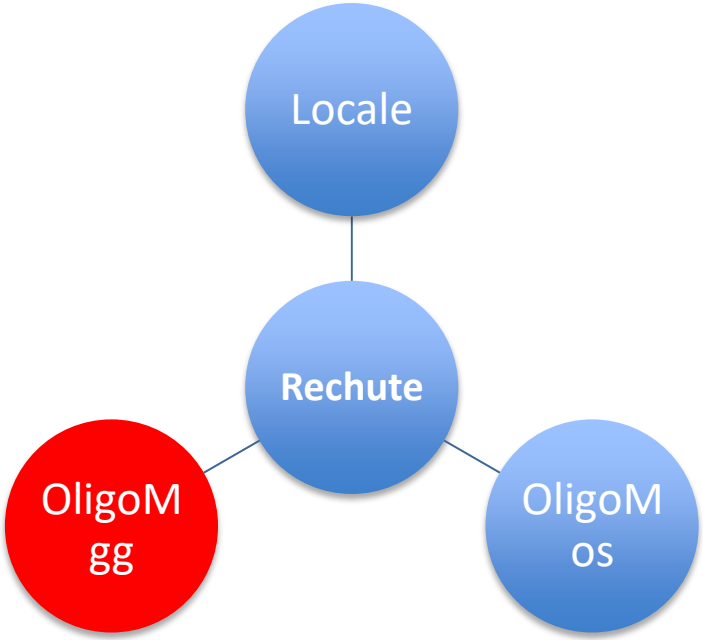


Fuller, D. B. *et al.* High-dose-rate stereotactic body radiation therapy for postradiation therapy locally recurrent prostatic carcinoma: Preliminary prostate-specific antigen response, disease-free survival, and toxicity assessment. *Practical Radiation Oncology* **5,** e615–23 (2015).





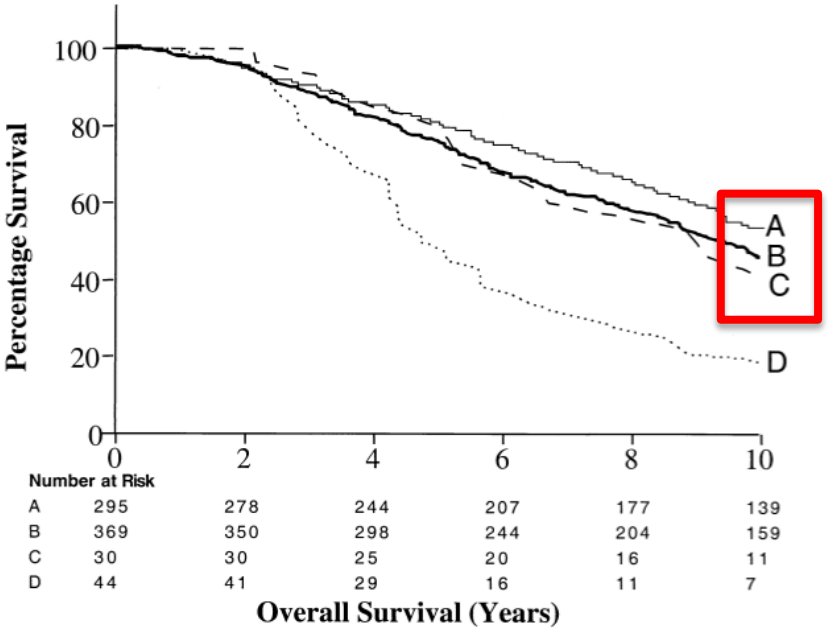

Local
stade
N+
M+


Locale
Rechute
OligoM gg
OligoM os

# Meilleure survie des cancers de prostate oligométastatiques

- Survie selon nb méta os:
  - ≤ 5 : 73% et 36% à 5 et 10 ans
  - > 5 : 45% et 18 %

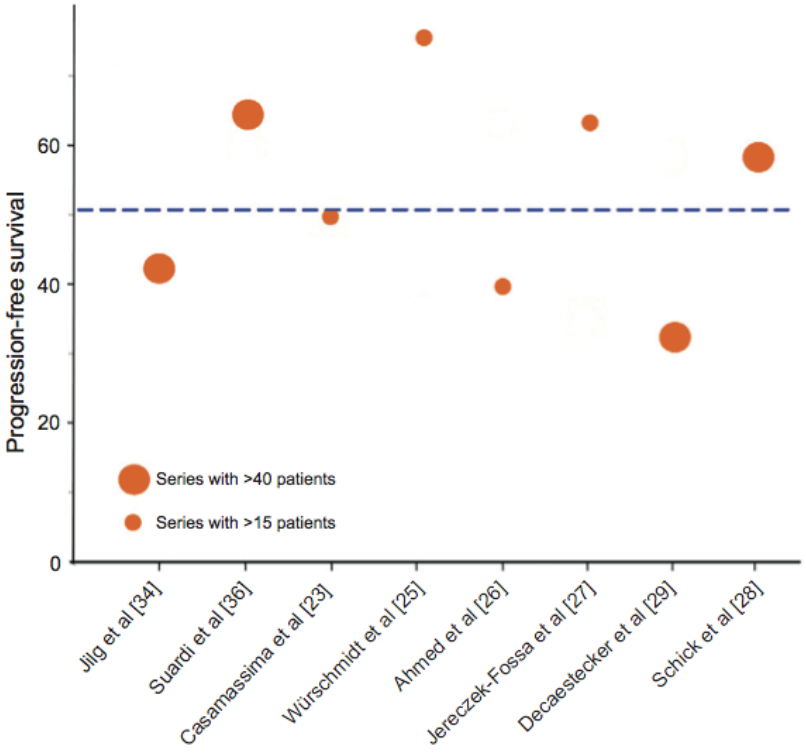
- Délai de 4,9 ans vs 3,3 ans au diagnostic de M+ osseuse si +/- 5M+




A : pas de méta
B : population globale
C : oligométastase ≤ 5
D : >5 méta

Singh et al. Is there a favorable subset of patients with prostate cancer who develop oligometastases?. IJROBP (2004) vol. 58 (1) pp. 3-10

# Rôle RT stéréotaxique dans oligométastases K prostate ?




- Près de 50% des patients sans progression biochimique à 1-3 ans

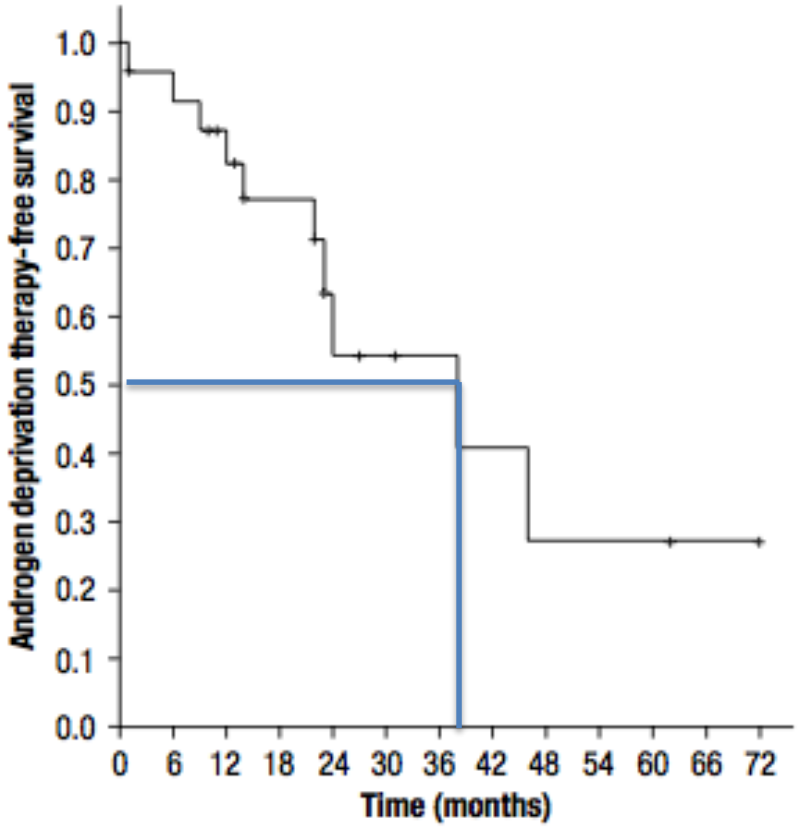

- Ost et al. Metastasis-directed Therapy of Regional and Distant Recurrences After Curative Treatment of Prostate Cancer: A Systematic Review of the Literature. European urology (2014)
- Bhattasali et al. Rationale for Stereotactic Body Radiation Therapy in Treating Patients with Oligometastatic Hormone-Naïve Prostate Cancer. Front. Oncol. (2013) vol. 3 pp. 293

# SBRT pour retarder HT

**24 pts : 11 M+ gg; 13 M+ os**
**SBRT : 50 Gy, 10f, Linac**

| At SBRT | |
|---|---|
| PSA (ng/mL) | |
| Median | 6.59 |
| Range | 0.34-72.9 |
| Age (years) | |
| Median | 67 |
| Range | 54-78 |
| Location of lesions, n (%) | |
| Bones | |
| Axial | 18 (37) |
| Nonaxial | 9 (18) |
| Lymph nodes | |
| Pelvic | 15 (31) |
| Extrapelvic | 7 (14) |

**Délai médian sans HT : 38 mois**




Berkovic et al. Salvage stereotactic body radiotherapy for patients with limited prostate cancer metastases: deferring androgen deprivation therapy. Clinical Genitourinary Cancer (2013) vol. 11 (1) pp. 27-32

# Peut-on guérir d'un cancer de prostate oligométastatique ?

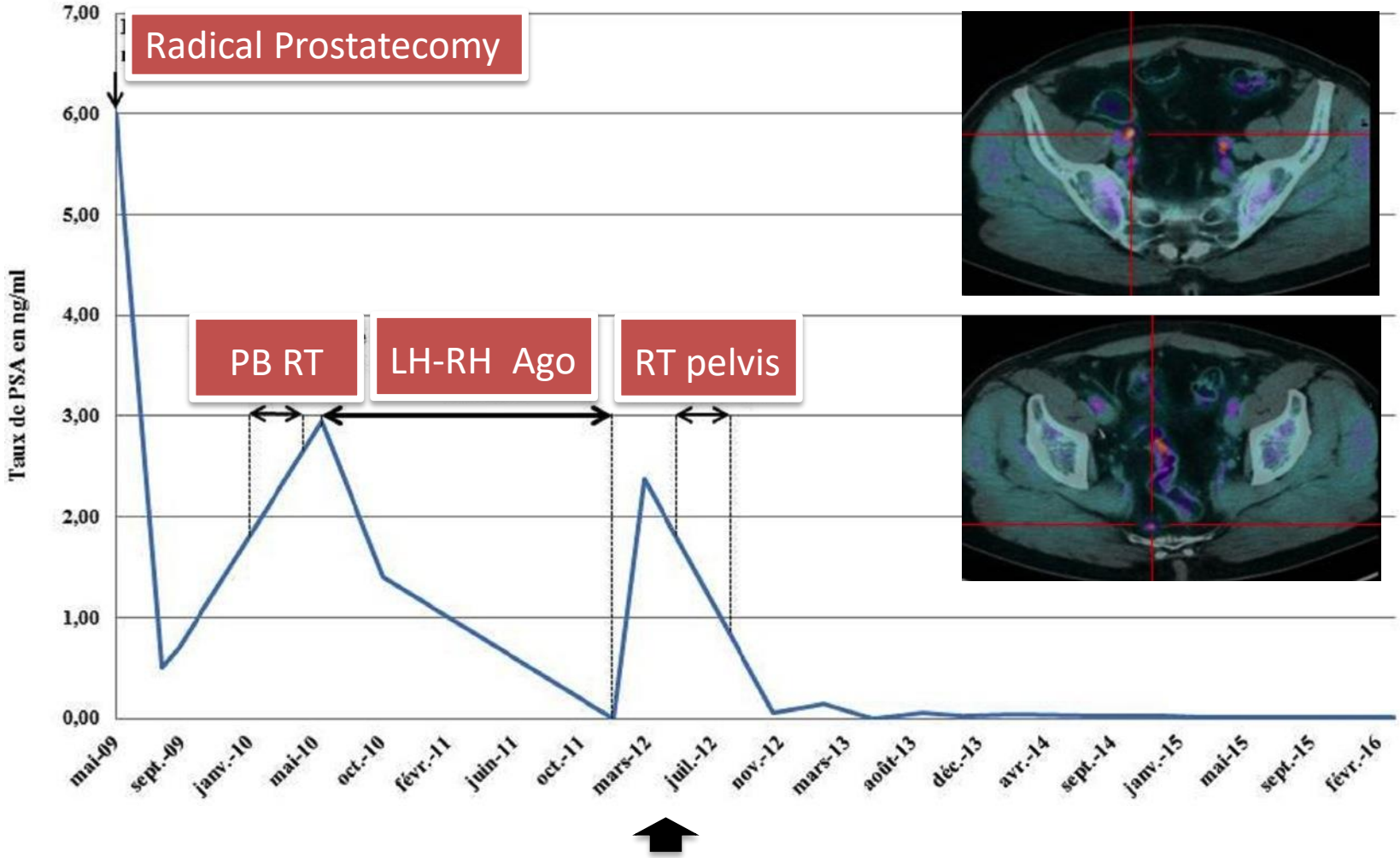
Eur J Nucl Med Mol Imaging (2014) 41:1267–1269
DOI 10.1007/s00259-014-2793-8

EDITORIAL COMMENTARY

## PET/CT imaging and the oligometastatic prostate cancer patient: an opportunity for a curative approach with high-dose radiotherapy?

**Raymond Miralbell · Franz Buchegger**

# Peut-on guérir d'un cancer de prostate oligométastatique ?




FCH PET : 2 pelvic LN

# Résultats Oligopelvis 1 GETUG P07 (Phase 2 )

- RT oligoM+ gg + 6 mois HT
  - 54 Gy 30 f gg pelviens
  - 66 Gy 30 f oligoM+
  - +/- loge 66 Gy 33f

- Pas de majoration tox aigue (GU ASCO 2016)
- Contrôle biochimique à 2 ans attendu 2018
- Faisabilité démontrée
- Recrutement rapide (20 mois)

Supiot *et al. BMC Cancer* (2015) 15:646
DOI 10.1186/s12885-015-1579-0

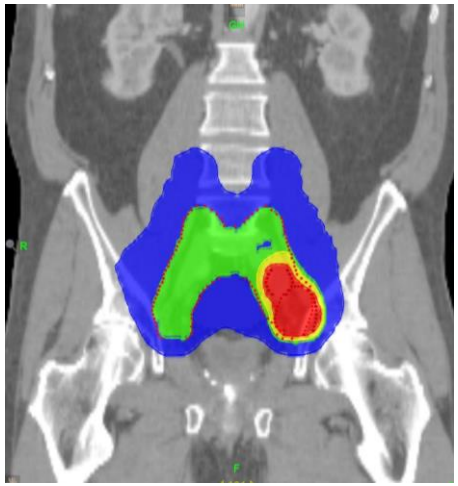
BMC Cancer

**STUDY PROTOCOL** **Open Access**

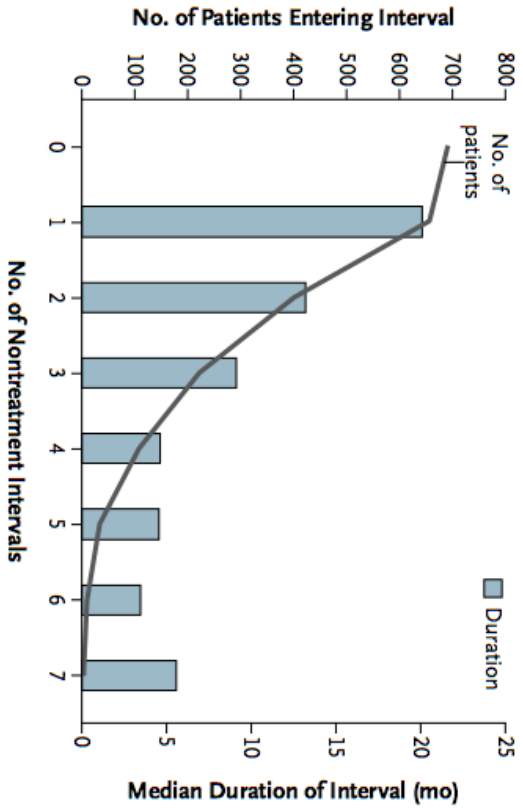
CrossMark

OLIGOPELVIS – GETUG P07: a multicentre phase II trial of combined salvage radiotherapy and hormone therapy in oligometastatic pelvic node relapses of prostate cancer

Stephane Supiot[1,2*], Emmanuel Rio[1], Valérie Pacteau[3], Marie-Hélène Mauboussin[3], Loïc Campion[2,4] and François Pein[3]



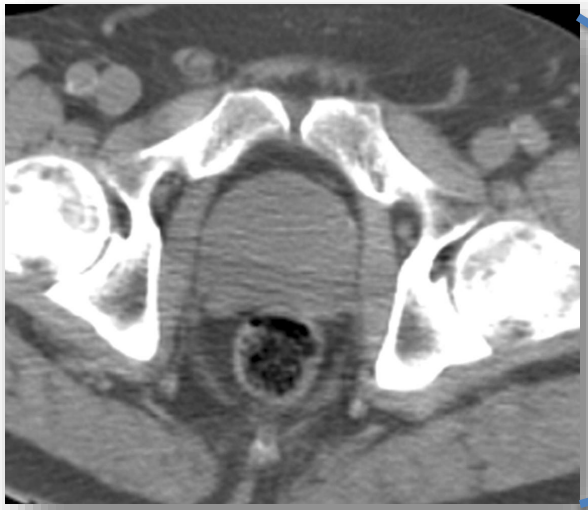
# Phase 3 PHRC 2017 : OLIGOPELVIS 2
# HT intermittente +/- RT dans oligoM+ gg

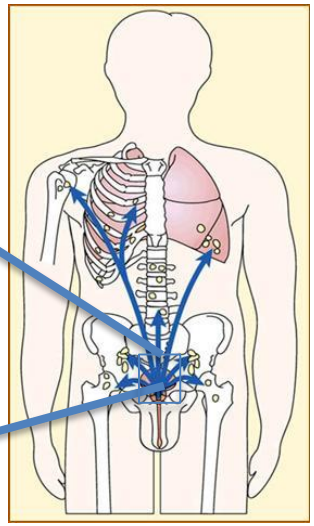


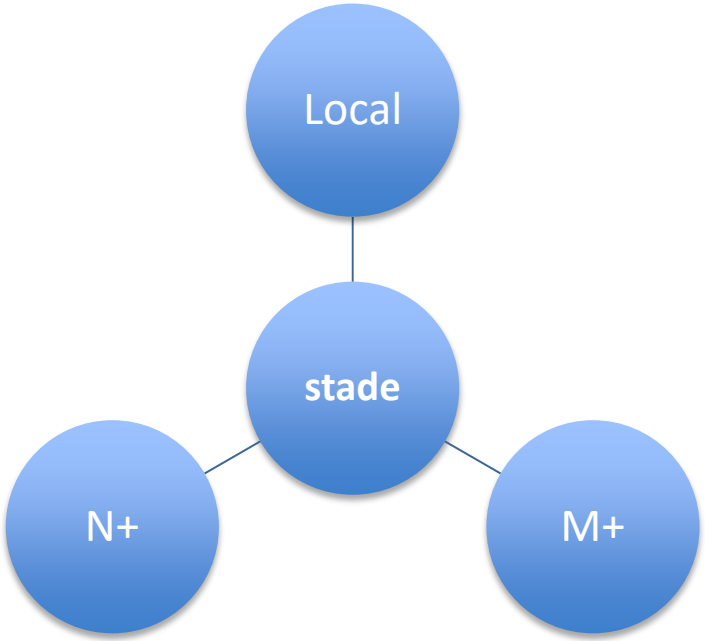

Stratifier selon $^{18}$FCH-PET, $^{68}$Ga-PSMA

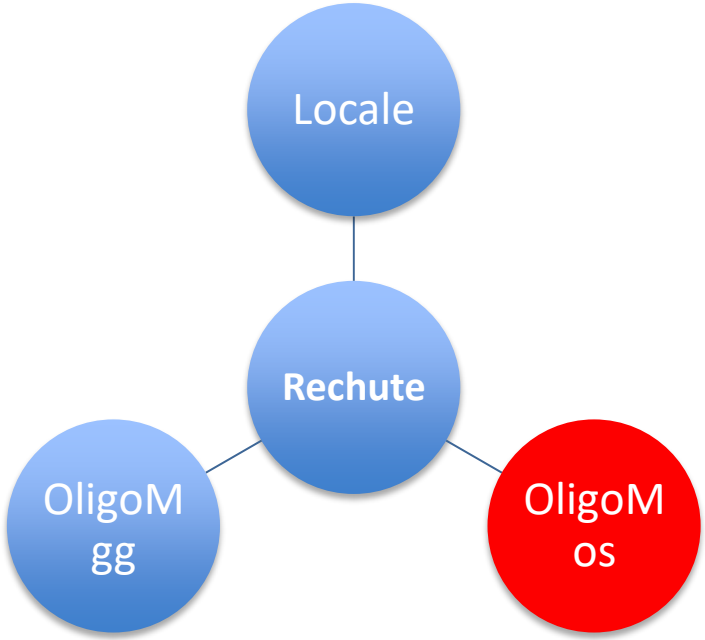
Crook et al. N Engl J Med (2012)

- HT = ttt std des métastases
- HT intermittente: 6 mois
- Reprise HT si PSA > 4 ng/ml
- Intervalle médian de reprise d'HT : 29 mois (Crook)
- **Hypothèse :**
- RT ganglionnaires pelviennes pourrait permettre de retarder la nécessité de réintroduire l'hormonothérapie
- Majorer temps à progression de 29 mois (IADT only) à 48 mois (IADT + salvage pelvic IG-IMRT) (HR=1.667).



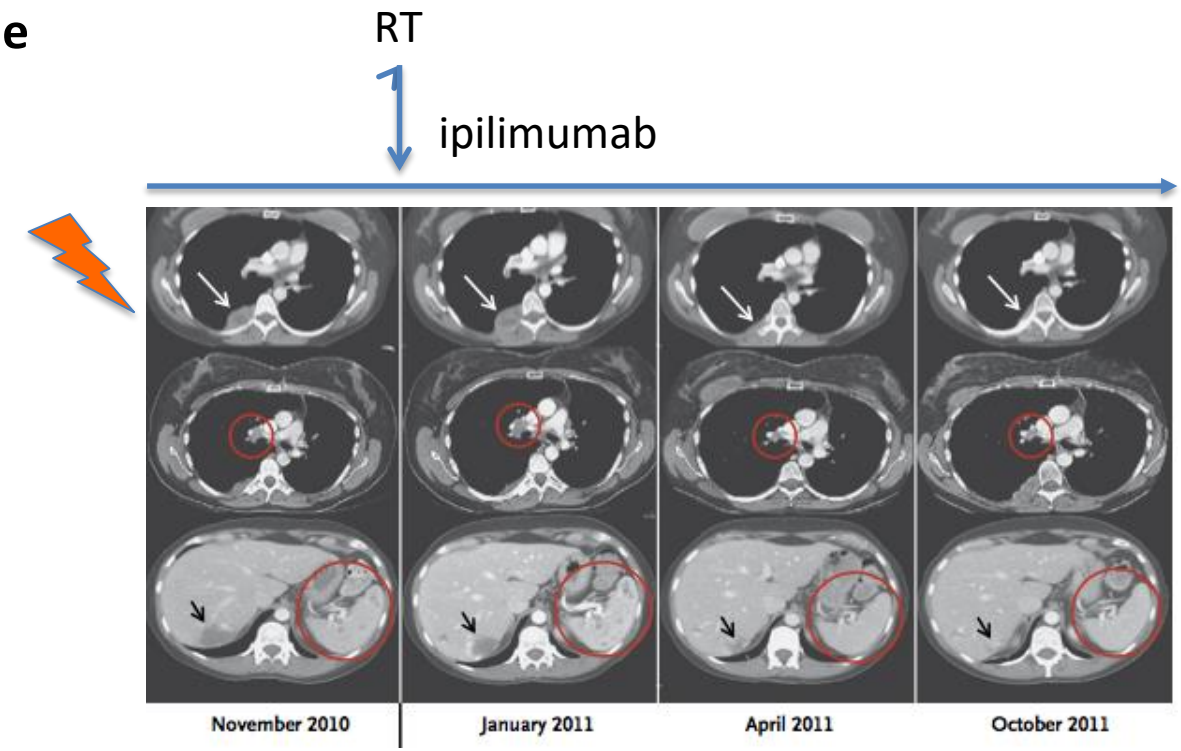



Local
stade
N+
M+


Locale
Rechute
OligoM gg
OligoM os

# Effet abscopal: RT stéréotaxique + immunothérapie

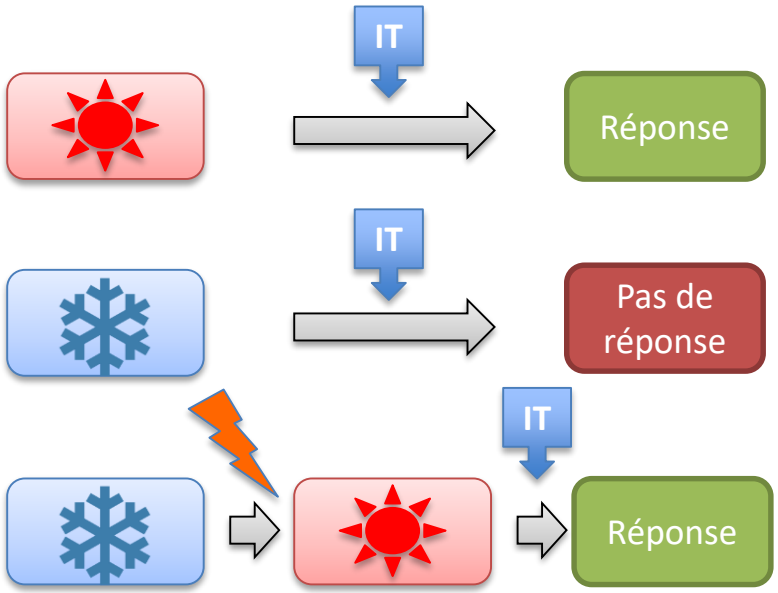
**Mélanome**




Postow et al. Immunologic correlates of the abscopal effect in a patient with melanoma. N Engl J Med (2012) vol. 366 (10) pp. 925-31

# Rationnel pour combiner RT + IT

## Majorer réponse IT par RT

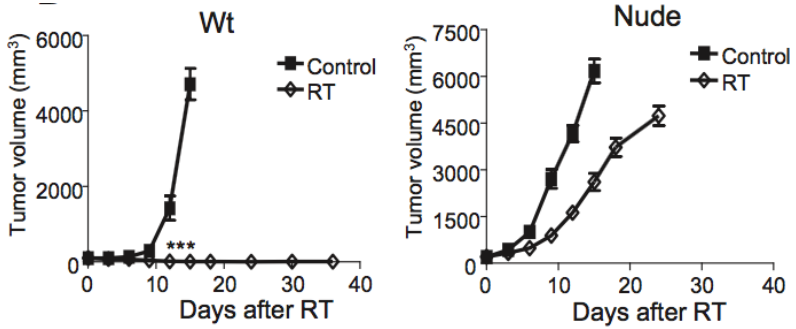



forte

faible

Réponse immunitaire anti-tumorale

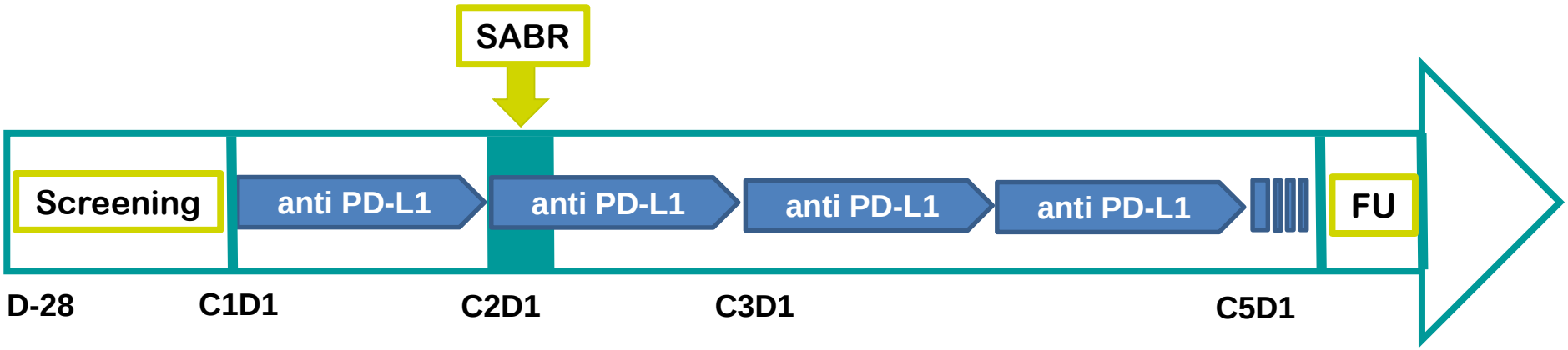
## Majorer réponse RT par IT





- Lee, Y et al. 2009. “Therapeutic Effects of Ablative Radiation on Local Tumor Require CD8+ T Cells: Changing Strategies for Cancer Treatment.” *Blood* 114(3): 589–95.
- Burnette et al. The efficacy of radiotherapy relies upon induction of type i interferon-dependent innate and adaptive immunity. Cancer research (2011) vol. 71 (7) pp. 2488-96

**POSTCARD : P**rostate cancer with **O**ligometa**ST**atic relapse : **C**ombining stereotactic **A**blative **R**adiotherapy and **D**urvalumab, a randomized phase II trial



# Phase II rando : RT stéréo + durvalumab

- Phase II randomisée
- TEP FCH : Oligométastases os ou gg (n<6)
- Pas d'hormonothérapie
- Pas d'atcd d'hormonothérapie dans les 2 ans auparavant

- **RT stéréo**
  - **os** 3x9 Gy J1 J3 J5
  - **gg** 3 X 11 Gy
- **anti PDL1 :** MEDI 4736 durvalumab (Astra-Zeneca) : ttt néoadjuvant 1 mois + concomitant + adjuvant (6 mois)
- **Pas d'HT**

- **Objectif principal :**
- Bras RT : contrôle biochimique à 1 an = 50%
- Bras RT + durva : 70%

- **Objectifs secondaires :**
  - Toxicité
  - Site de rechute
  - Réponse immunologique
  - Cellules tumorales circulantes
  - Sphingolipides circulants

- 70 (RT + durva) +35 (RT) patients à inclure

# Conclusion

# Imagerie nucléaire

## = partenaire de plus en plus indispensable RT K de prostate

- **Mieux définir le stade initial de la maladie**
- **Mieux définir le siège de la rechute**