Dr Manon KISSEL
Praticien Radiothérapeute
Institut Curie Paris

Curiethérapie prostatique de rattrapage

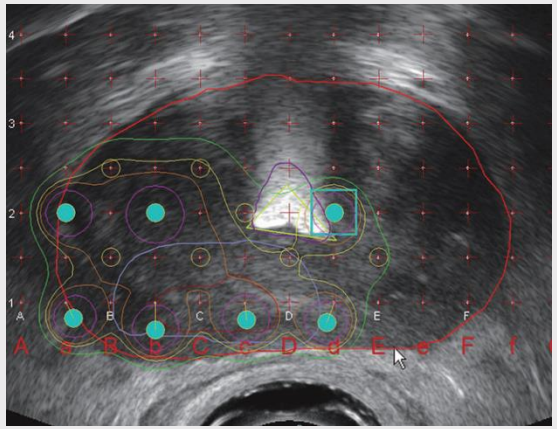
ENSEMBLE, PRENONS LE CANCER DE VITESSE

institut Curie

Rationnel

- Rechute locale isolée après RTE haute dose : 8,5% des patients
- Rechute locale après RTE pour K à haut risque : associée à la rechute métastatique et à l'OS
- Traitement historique : prostatectomie de rattrapage
  - Mais toxique sur le plan urinaire
- Réirradiation avec techniques classiques : toxique ++
- Au final : souvent hormonothérapie
- Curiethérapie : profil de distribution de la dose très favorable

	No. of patients (%)	
Salvage therapy	**Primary RP (N = 620)**	**Primary EBRT (N = 430)**
Androgen deprivation	367 (59.2)	402 (93.5)
EBRT	248 (40.0)	8 (1.9)
Cryotherapy	3 (0.5)	13 (3.0)
Radical prostatectomy	NA	4 (0.9)
Brachytherapy	NA	1 (0.2)
Unknown	2 (0.3)	2 (0.5)



Agarwal P., Cancer 2007
Zumsteg ZS., J Urol 2016
Zilli T., IJROBP 2016

institut Curie

Evidence ?

HDR

4 études prospectives

Auteur Année	N	Design
Lee 2007	21	Rétrospective
Tharp 2008	7	Rétrospective
Lyczek 2009	115	Rétrospective
Jo 2011	11	Rétrospective
Chen 2013	52	Rétrospective
Yamada 2014	42	Prospective Ph2
Wojcieszek 2016	83	Rétrospective
Mbeutcha 2017	10	Rétrospective multicentrique
Kollmeier 2017	61	Rétrospective
Baumann 2017	8	Rétrospective
Jiang 2017	22	Rétrospective
Maenhout 2017	17	NR
Murgic 2018	15	Prospective
Lopez 2019	75	Rétrospective multicentrique
Chitmanee 2020	50	Prospective
Slevin 2020	43	Rétrospective
Van Son 2021	150	Prospective

LDR

2 études prospectives

Auteur Année	N	Design
Loening 1993	31	Rétrospective
Beyer 1999	17	Rétrospective
Grado 1999	49	Rétrospective
Koutrouvelis 2003	31	Rétrospective
Wong 2006	17	Rétrospective
Nguyen 2007	25	Prospective Ph2
Aaronson 2009	24	Rétrospective
Burri 2010	37	Rétrospective
Moman 2010	31	Rétrospective
Hsu 2013	15	Rétrospective
Henriquez 2014	56	Rétrospective
Peters 2014	20	Rétrospective
Vargas 2014	69	Rétrospective
Rose 2015	18	Rétrospective
Lacy 2016	21	Rétrospective
Barbara 2017	19	Rétrospective
Kollmeier 2017	98	Rétrospective
Crook 2019	92	Prospective

institut Curie

Evidence ?

	Age (yr)	Whole-gland salvage (%)	Biopsy-proven recurrence (%)	Presalvage PSA (ng/mL)	Perisalvage ADT use (%)	Interval from initial treatment to recurrence or salvage (mo)	Median follow-up (mo)	Number of studies (*n*)	Number of patients (*n*)
RP	65	100	99	6.0	16	50	47	52	2686
Cryotherapy	66	93	99	5.8	35	63	32	32	5153
HIFU	69	86	100	5.0	18	63	33	20	1783
SBRT	72	61	81	4.0	37	89	26	8	261
HDR	71	85	94	4.5	43	61	40	16	586
LDR	69	92	95	5.5	37	67	52	32	853

ADT = androgen deprivation therapy; HDR = high-dose-rate brachytherapy; HIFU = high-intensity focused ultrasound; LDR = low-dose-rate brachytherapy; PSA = prostate-specific antigen; RP = radical prostatectomy; SBRT = stereotactic body radiotherapy.

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Review – Prostate Cancer
Editorial by XXX on pp. x–y of this issue

A Systematic Review and Meta-analysis of Local Salvage Therapies After Radiotherapy for Prostate Cancer (MASTER)

Luca F. Valle[a,†], Eric J. Lehrer[b,†], Daniela Markovic[c], David Elashoff[c], Rebecca Levin-Epstein[a], R. Jeffery Karnes[d], Robert E. Reiter[e], Matthew Rettig[f,g], Jeremie Calais[h], Nicholas G. Nickols[a,i], Robert T. Dess[j], Daniel E. Spratt[j], Michael L. Steinberg[a], Paul L. Nguyen[k], Brian J. Davis[l], Nicholas G. Zaorsky[m], Amar U. Kishan[a,e,]*

Méta-analyse MASTER
150 études

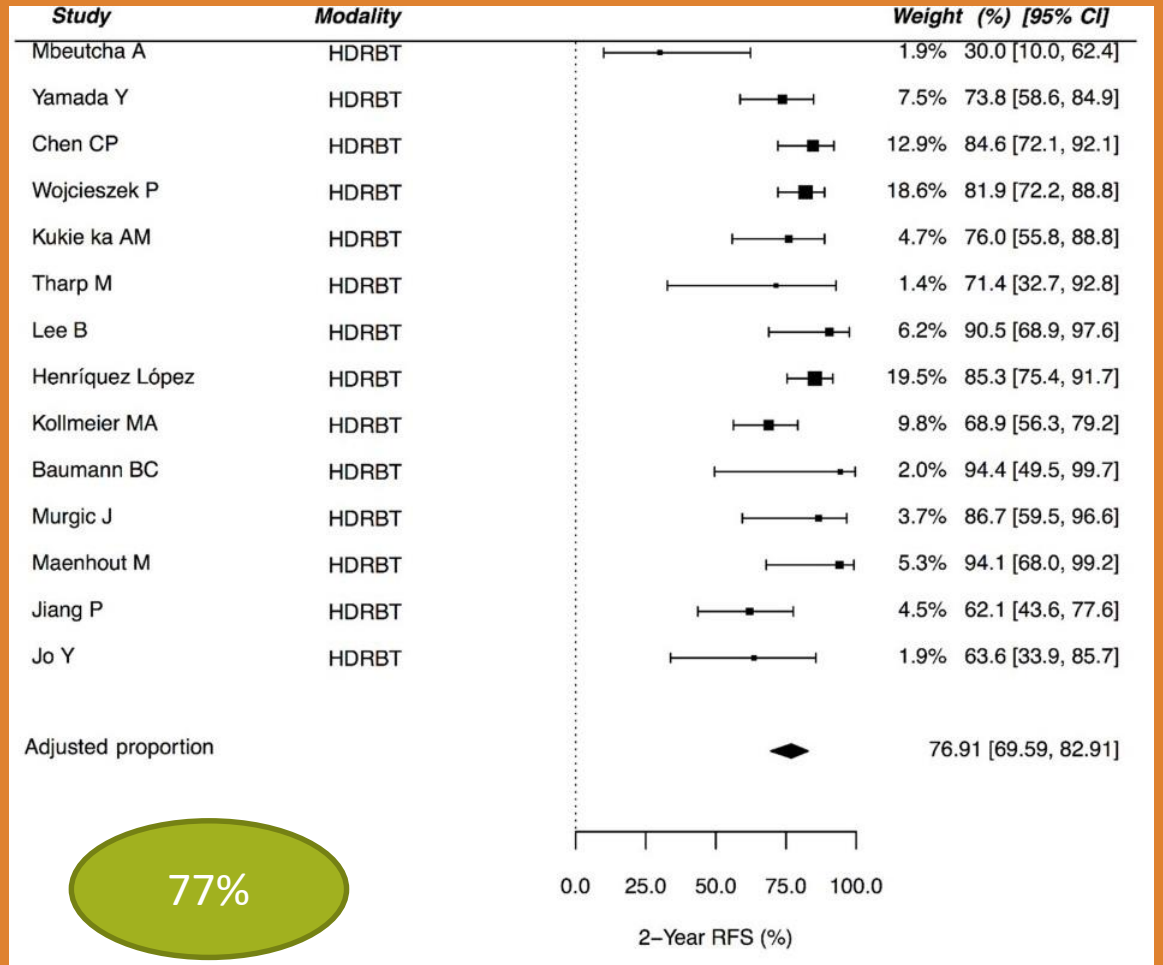
Valle L., Eur Urol 2020

institut Curie

HDR versus LDR

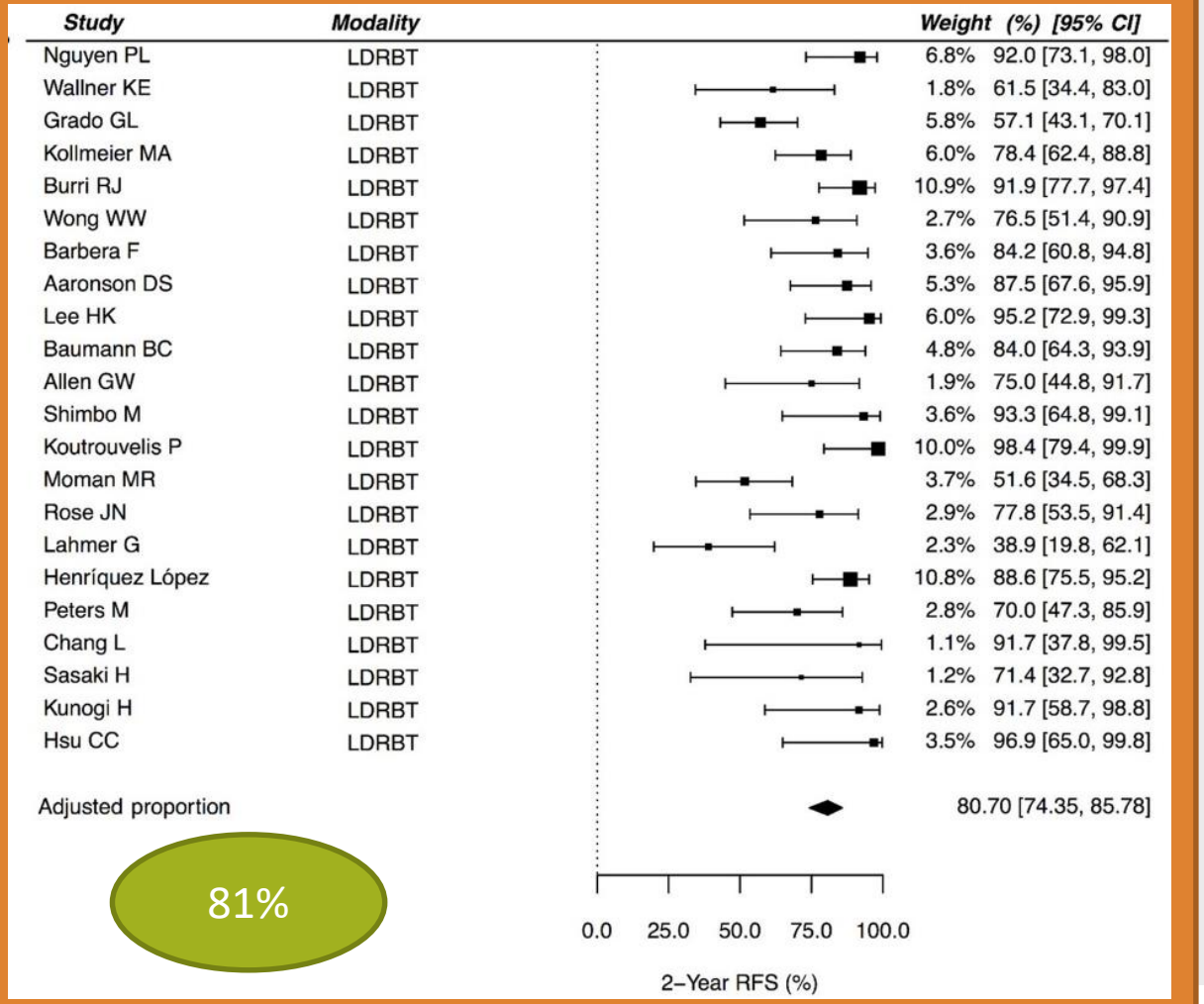
bPFS 2 ans

HDR



77%

LDR



81%

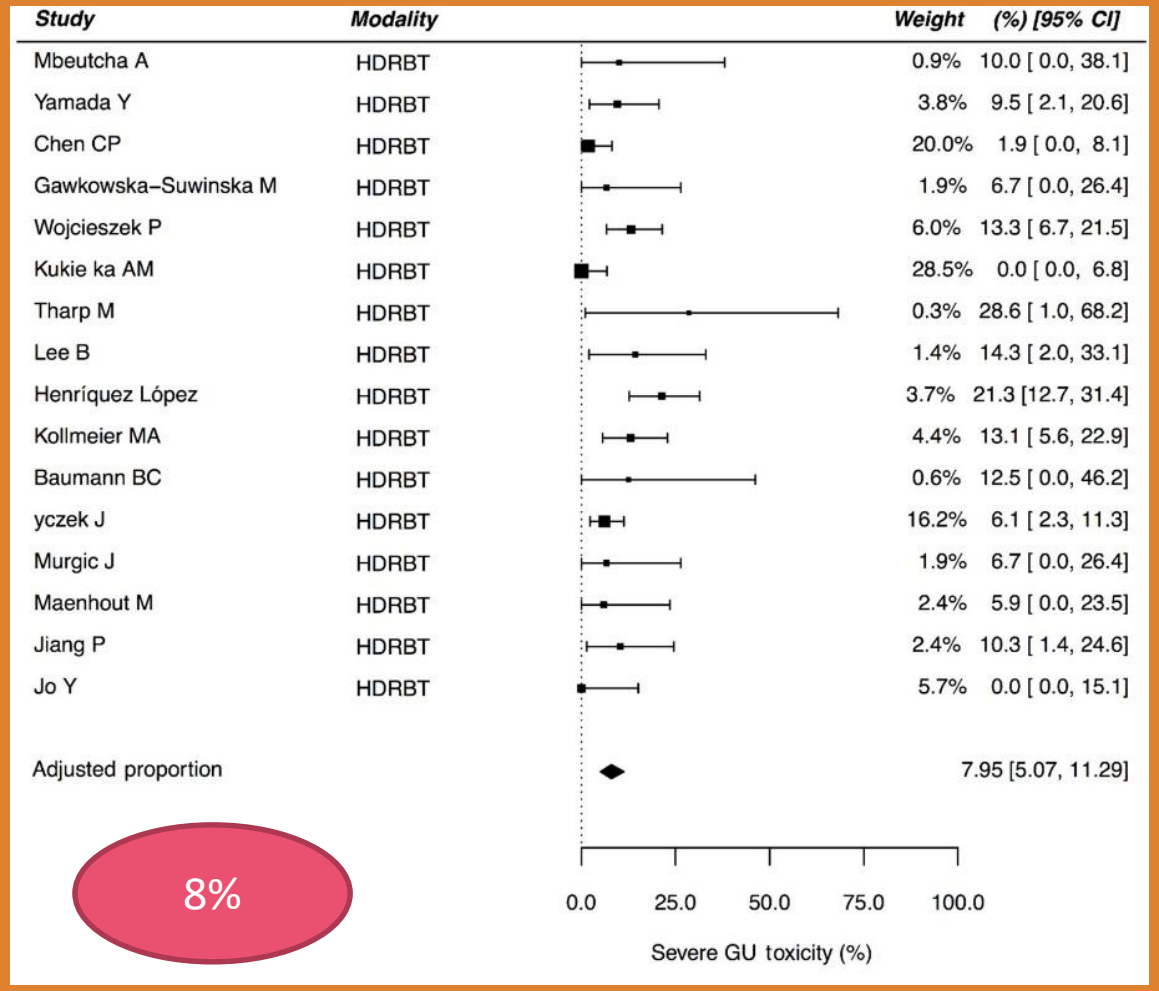
Valle, Eur Urol 2020

institut Curie

HDR versus LDR

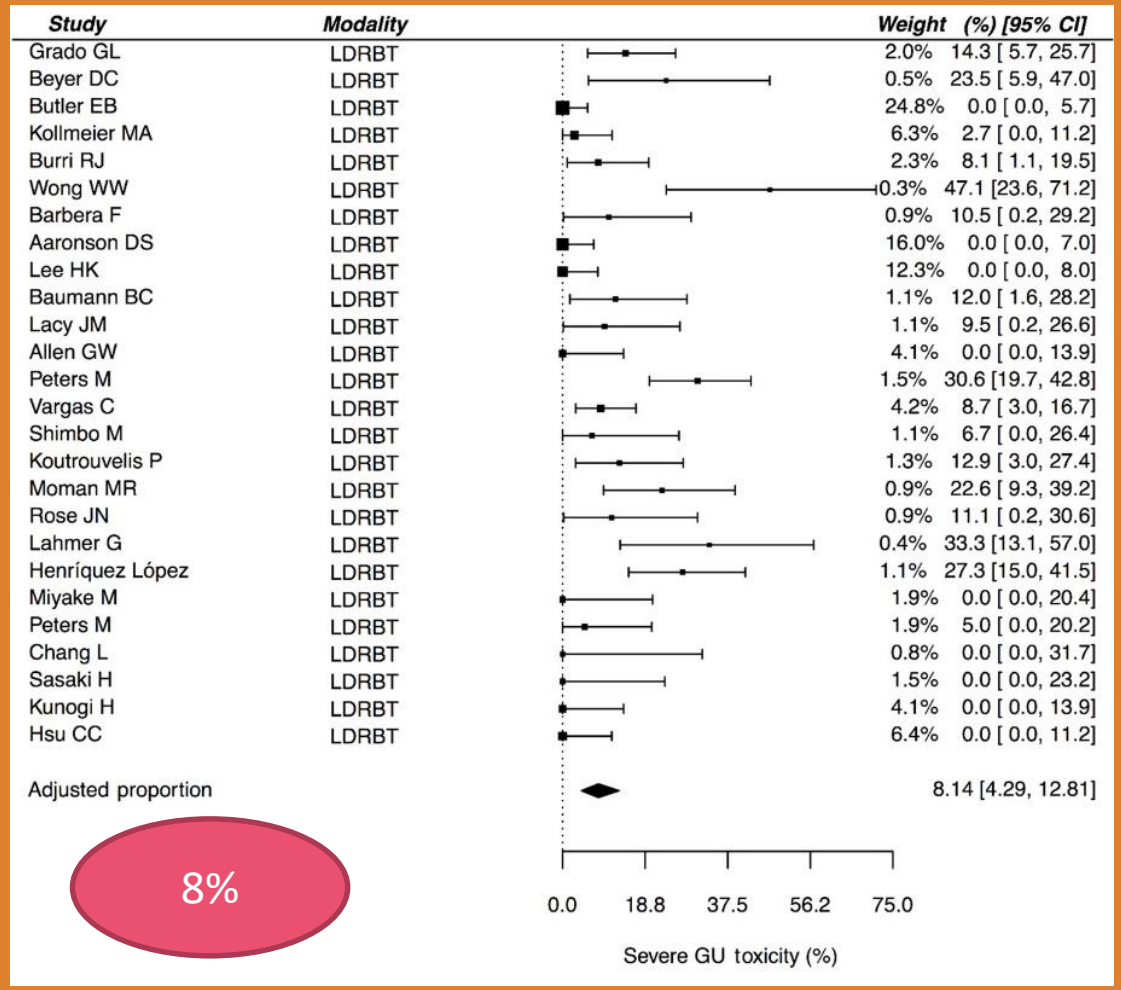
Tox GU sévère

HDR



8%

LDR



8%

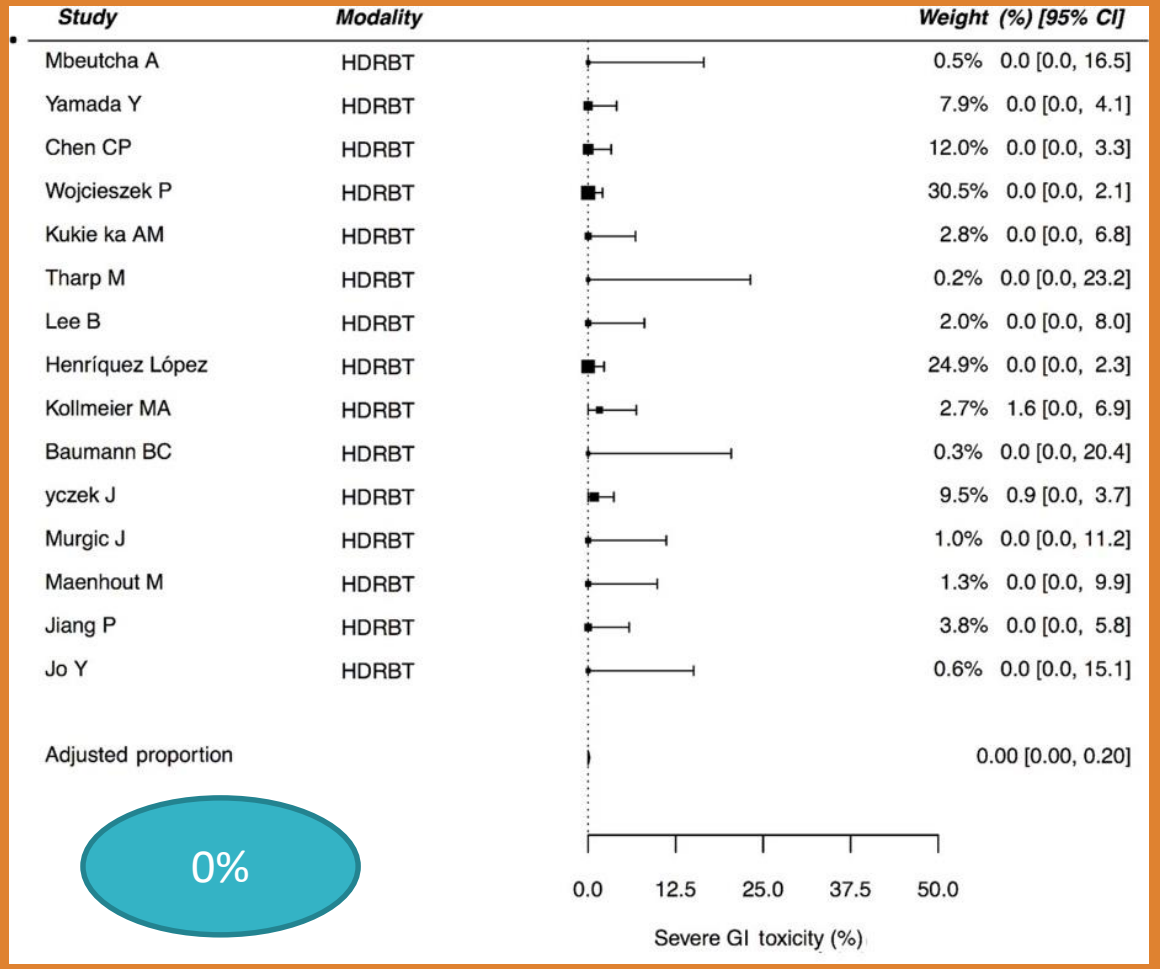
Valle, Eur Urol 2020

institut Curie

HDR versus LDR

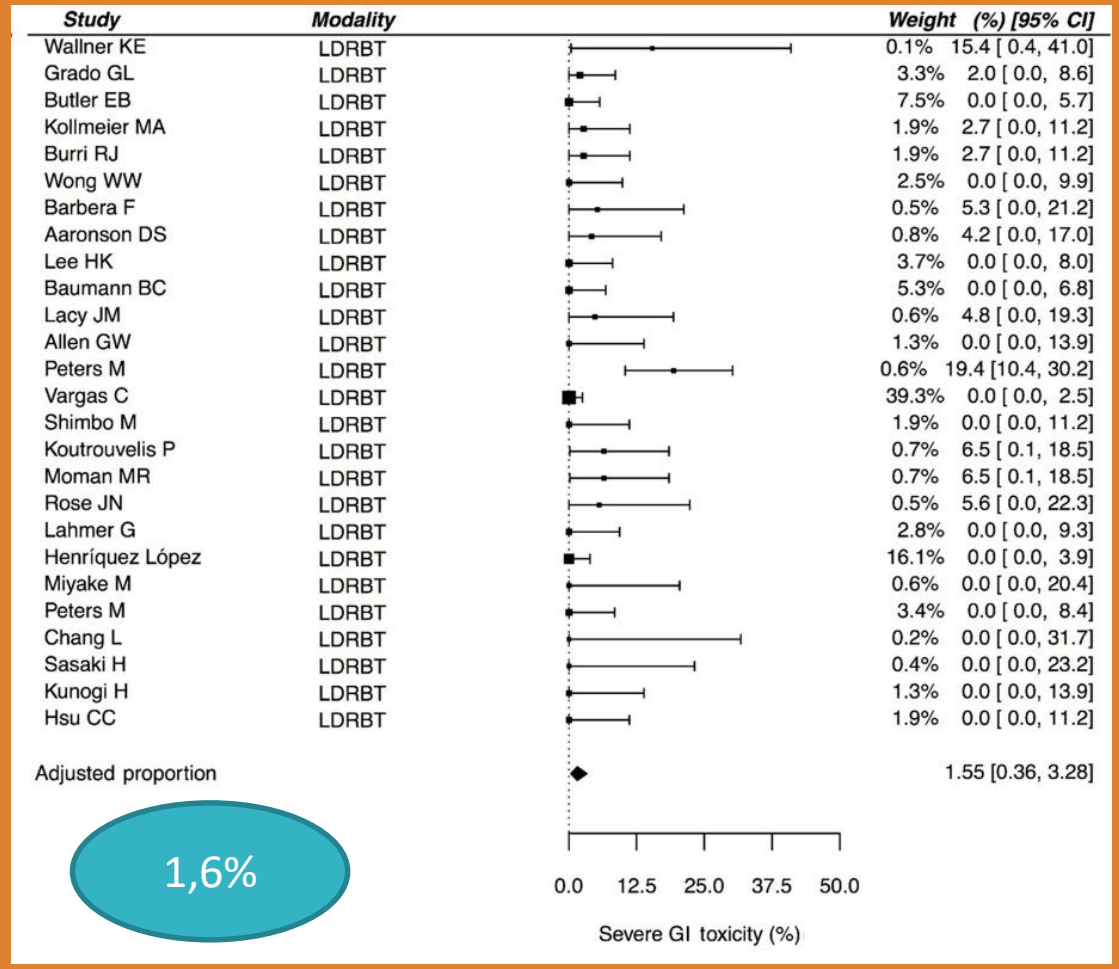
Tox GI sévère

HDR



0%

LDR



1,6%

Valle L., Eur Urol 2020

institut Curie

Comparaison aux autres traitements de rattrapage

	2-yr RFS	5-yr RFS	Severe GU toxicity	Severe GI toxicity
Radical prostatectomy				
Adjusted percent[a] (95% CI)	72% (66–78%)	53% (46%–59%)	21% (16%–26%)	1.5% (0.4%–3.2%)
Odds ratio (95% CI)	1.0	1.0	NA	NA
p value	Reference	Reference	Reference	Reference
R^2 (%)	0.0	0.0	0.0	0.0
Cryotherapy				
Adjusted percent[a] (95% CI)	66% (59–72%)	57% (49–65%)	15% (8–23%)	0.9% (0.3–1.8%)
Odds ratio (95% CI)	0.74 (0.49–1.12)	1.20 (0.80–1.79)	NA	NA
p value	0.2	0.4	0.2	0.5
R^2 (%)	25	0.0	8.2	27
HIFU				
Adjusted percent[a] (95% CI)	52% (45%–59%)	46% (37%–55%)	23% (17%–30%)	0.8% (0.1%–2.1%)
Odds ratio (95% CI)	0.42 (0.28–0.64)	0.76 (0.48–1.21)	NA	NA
p value	<**0.001**	0.2	0.5	0.4
R^2 (%)	0.0	41	15	22
HDR				
Adjusted percent[a] (95% CI)	77% (69–83%)	58% (52–64%)	9.6% (6.0–13.9%)	0.0% (0.0–0.3%)
Odds ratio (95% CI)	1.26 (0.77–2.09)	1.25 (0.88–1.78)	NA	NA
p value	0.4	0.2	**0.002**	**0.003**
R^2 (%)	0.0	91	0.0	0.0
LDR				
Adjusted percent[a] (95% CI)	79% (72–85%)	53% (43–63%)	9.1% (5.2–14%)	2.1% (0.6–4.0%)
Odds ratio (95% CI)	1.49 (0.89–2.50)	1.02 (0.63–1.67)	–	–
p value	0.13	0.9	**0.001**	0.6
R^2 (%)	4.3	5.2	12	20%

Survie sans rechute pas de différence significative par rapport à la PR

Toxicité GU sévère : la curie fait bien mieux que les autres techniques

Toxicité GI sévère : le HDD fait mieux

Valle L., Eur Urol 2020

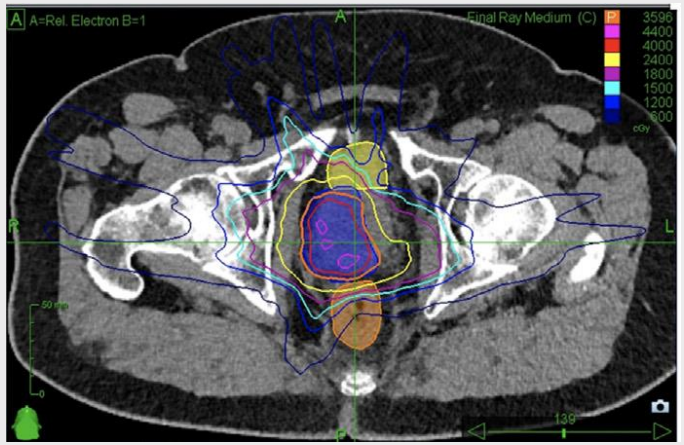
institut Curie

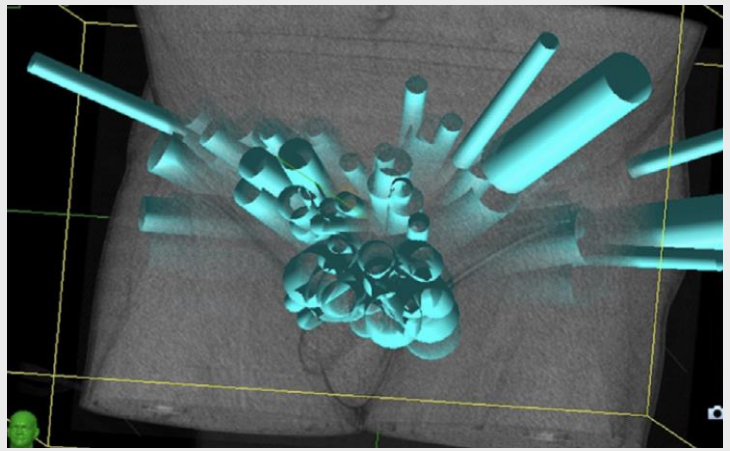
Versus SBRT ?

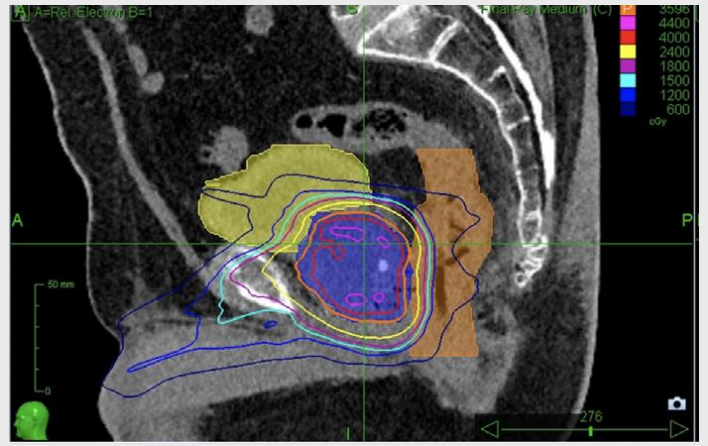
SBRT				
Adjusted percent[a] (95% CI)	58% (46–69%)	56% (37–73%)	5.6% (1.4–12%)	0.0% (0.0–1.2%)
Odds ratio (95% CI)	0.52 (0.30–0.93)	1.13 (0.50–2.58)	NA	NA
p value	0.03	0.8	<**0.001**	0.07
R^2 (%)	55	4.2	0.00	0.0
HDR				
Adjusted percent[a] (95% CI)	77% (69–83%)	58% (52–64%)	9.6% (6.0–13.9%)	0.0% (0.0–0.3%)
Odds ratio (95% CI)	1.26 (0.77–2.09)	1.25 (0.88–1.78)	NA	NA
p value	0.4	0.2	**0.002**	**0.003**
R^2 (%)	0.0	91	0.0	0.0
LDR				
Adjusted percent[a] (95% CI)	79% (72–85%)	53% (43–63%)	9.1% (5.2–14%)	2.1% (0.6–4.0%)
Odds ratio (95% CI)	1.49 (0.89–2.50)	1.02 (0.63–1.67)	–	–
p value	0.13	0.9	**0.001**	0.6
R^2 (%)	4.3	5.2	12	20%

Survie sans rechute : idem curie à 5 ans

Toxicités : profil favorable







Valle, Eur Urol 2020
Baty, Cancer Radiothérapie 2019

institut Curie

Versus SBRT ?

	Age (yr)	Whole-gland salvage (%)	Biopsy-proven recurrence (%)	Presalvage PSA (ng/mL)	Perisalvage ADT use (%)	Interval from initial treatment to recurrence or salvage (mo)	Median follow-up (mo)	Number of studies (*n*)	Number of patients (*n*)
RP	65	100	99	6.0	16	50	47	52	2686
Cryotherapy	66	93	99	5.8	35	63	32	32	5153
HIFU	69	86	100	5.0	18	63	33	20	1783
SBRT	72	61	81	4.0	37	89	26	8	261
HDR	71	85	94	4.5	43	61	40	16	586
LDR	69	92	95	5.5	37	67	52	32	853

Dose volume constrains for prostate stereotactic body radiotherapy in case of reir-radiation with CyberKnife®.

Organs at risk	Dose–volume constraints		
	Dose	Volume	Maximal dose
Rectum wall	27 Gy	2 cm^3	
	12 Gy	20%	
Bladder wall	27 Gy	5 cm^3	
	12 Gy	15%	
Urethra + 3 mm	24 Gy	< 30%	39 Gy
	36	1 cm^3	

GETUG-AFU 31 en cours

La plus grosse série :
Lille
100 Patients
Multicentrique
36Gy/6 fractions 1j/2
Follow-up : 29 mois

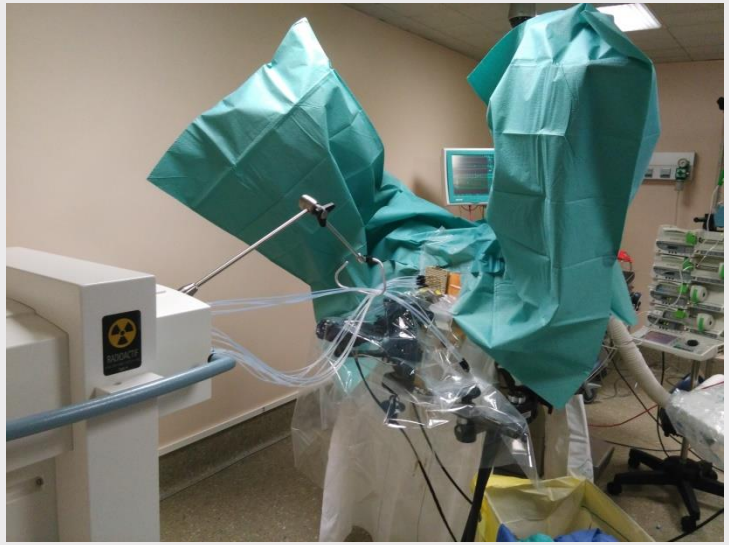
Moins de données
Moins de recul

Mais données actuelles rassurantes
Pas les contraintes d'éligibilité à la curiethérapie (anesth, volume)
Accessibilité ++

Valle, Eur Urol 2020
Pasquier D., IJROBP 2019
Pasquier D., BMJ Open 2019

institut Curie

Curiethérapie de rattrapage en pratique



Focale, partielle, whole-gland ?
Quelle dose ?
Association à une hormono courte / longue ?
Contraintes de dose aux OAR ?
Spacer ?

- Technique idem curiethérapie primo-traitement
- /!\ Sélection des patients
  - Etat général et comorbidités
  - Bilan d'extension rigoureux prouvant le caractère isolé de la rechute
  - Vérifier l'absence de séquelle de l'irradiation antérieure
  - Biopsies +++
  - Facteurs pronostiques : PSA à la rechute, PSAdt, intervalle libre, haut risque initial

Kaljouw E., Radiotherapy and Oncology 2016

institut Curie

Auteur Année	N	Design	Proportion de haut risque initial	PSA médian à la rechute (ng/mL)	$EQD2_{1,5}$ curie de rattrapage (Gy)	Volume traité	Utilisation hormono
Chen 2013	52	Rétrospective	NR	5	77,1	Whole-gland	46%
Chitmanee 2020	50	Prospective	38%	NR	111,3	Focal	8%
Jiang 2017	22	Rétrospective	54,5%	4	98,6	Focal + ZP	18%
Lee 2007	21	Rétrospective	62%	5,9	77,1	Whole-gland	52%
Lopez 2019	75	Rétrospective multicentrique	30%	4,1	220	Whole-gland	29%
Lyczek 2009	115	Rétrospective	NR	NR	98,6	NR	100%
Maenhout 2017	17	NR	24%	4,8	111,3	Focal	NR
Murgic 2018	15	Prospective	14%	4,1	115,7	Focal	0%
Slevin 2020	43	Rétrospective	30%	3,1	111,3	Focal	65%
Van Son 2021	150	Prospective	NR	NR	111,3	Focal	NR
Wojcieszek 2016	83	Rétrospective	35%	3,1	98,3	Whole-gland	53%
Yamada 2014	42	Prospective Ph2	NR	3,5	86,9	Whole-gland	43%
Mbeutcha 2017	10	Rétrospective multicentrique	70%	4,4	85	Whole-gland	20%
Tharp 2008	7	Rétrospective	0%	5,5	51	Whole-gland	100%
Kollmeier 2017	61	Rétrospective	NR	3,9	86,9	Whole-gland	44%
Baumann 2017	8	Rétrospective	55%	5	55,7	Whole-gland	100%
Jo 2011	11	Rétrospective	45%	5,8	78,6	Focal	0%

Contraintes de dose ?

- LDR : issues du RTOG0526
- HDR : moins consensuel
- « Standard ou ajustées »

HDR

V100 > 90%
D90 > 100%
Urètre D10 < 115-120%
Rectum D10 < 70% -100%

LDR ^{125}I

Crook et al. :
V150 < 45%
V200 < 10%
Pas de contraintes OAR

UCSF :
D90 > 100%
Vessie – Rectum : V125% < 1cc
Urètre : V125% < 1cc

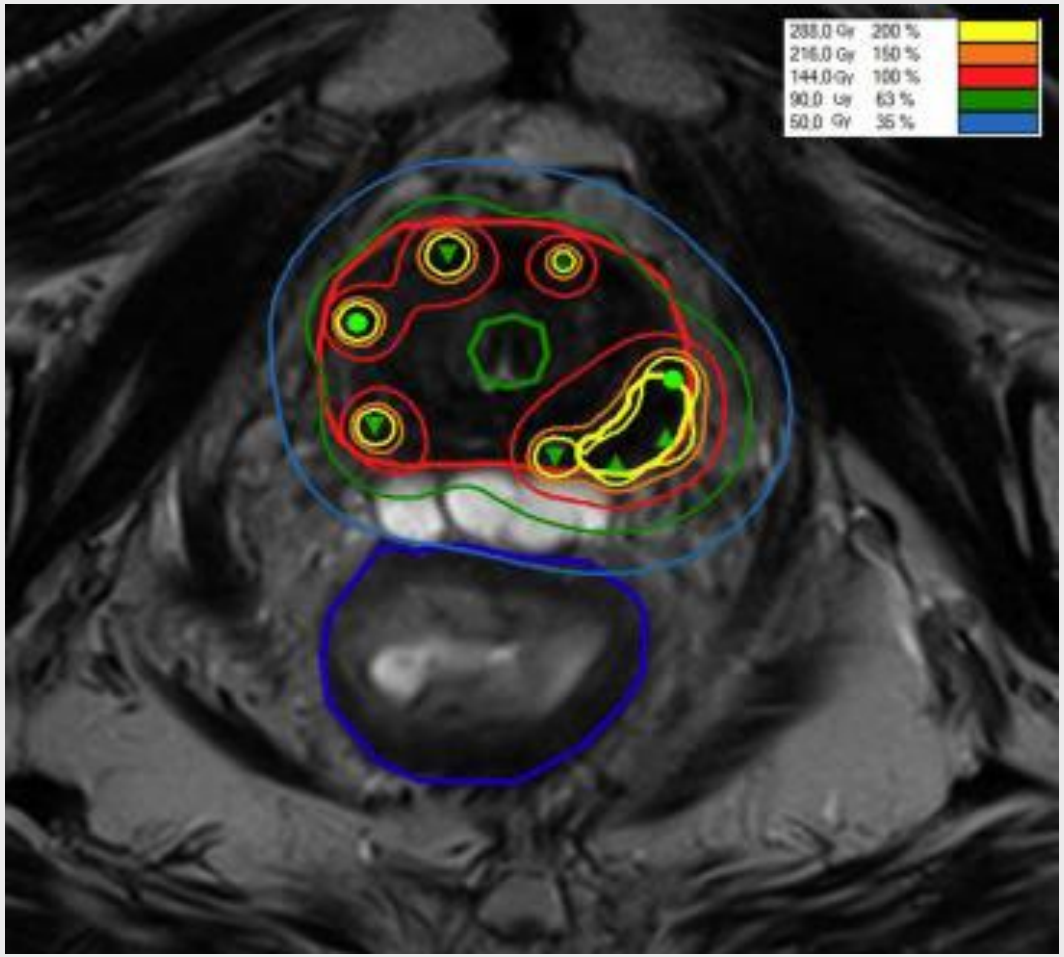
Crook J. IJROBP 2018
Kaljouw E., Radiotherapy and Oncology 2016

institut Curie

Spacer ?

- Réduction significative de la dose à la paroi rectale
- D0,1cc : 63.3 Gy (29.0–78.3) vs. 83.9 Gy (34.9–180.0) (*p* = 0.04)
- Mais : risque plus élevé d'échec de pose du spacer (fibrose ++)
- Une fistule rapportée dans la littérature dans ce contexte

Pertinence clinique au vu des taux de toxicité GI sévère ?



Guimas V. et al, Brachytherapy 2016
Vaggers S. et al, World J Urol 2020

institut Curie

Recommandations actuelles

Recommendations for prostate salvage reirradiation depending on the expert societies.

Expert societies	Recommendations of salvage reirradiation
Gec-ESTRO [60]	Considering brachytherapy: (% of agreement): ECOG/WHO performance score of 0 or 1 (89%); ≤T3b both at primary and at time of relapse (81%); Gleason score at primary treatment ≤8 (95%); maximum of International Prostate Score Symptom (IPSS) from 8 to 15 (88%); 12–24 biopsy should be performed at relapse (83%)
Afu [18]	Considering brachytherapy: high- or low-dose-rate brachytherapy possible, keeping in mind the few and retrospective data. The potential toxicity (genitourinary particularly) must be discussed with the patient. There is no consensus for the modalities of implantation and constraints of organs at risk
EAU [17]	Considering reirradiation and salvage treatment: although there is no role for salvage external beam radiotherapy following local recurrence after previous definitive radiotherapy, in carefully selected patients with a good performance score, primary localized prostate cancer and histologically proven local recurrence, high- or low-dose-rate brachytherapy remain effective treatment options with an acceptable toxicity profile; do not offer high-intensity focused ultrasound, cryosurgical ablation or salvage brachytherapy to patients with proven local recurrence since it is still experimental; salvage radical prostatectomy should only be performed in experienced centres
FROGG [61]	Salvage therapy for local relapse post-radiotherapy should only be considered in men with biopsy-confirmed, isolated local prostate recurrence who are of good performance status with minimal comorbidities and a life expectancy greater than 10 years. Suitable treatment options include observation, immediate or deferred androgen deprivation, or local salvage therapy (including radical prostatectomy, brachytherapy, stereotactic body radiotherapy, high-intensity focused ultrasound, cryotherapy). Suitable patients should be considered for clinical trials

…uriethérapie (European group of brachytherapy); ESTRO: Euro… …peutic Radiation Oncology; ECOG… …ld Health Organizati… …sociation française d'urolog… …); EAU: Eu… …ia… …Urinary…

Sélection des patients ++ : OMS, espérance de vie, éviter les hauts risques

Biopsies à la rechute

Efficace

Profil de toxicité favorable

Pas de consensus sur les modalités ni sur les contraintes de dose

Discussion avec le patient

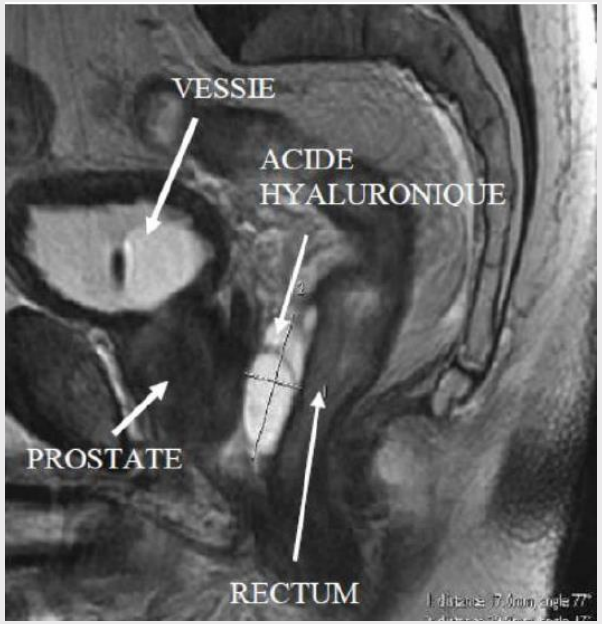
Garder en tête le faible niveau de preuve

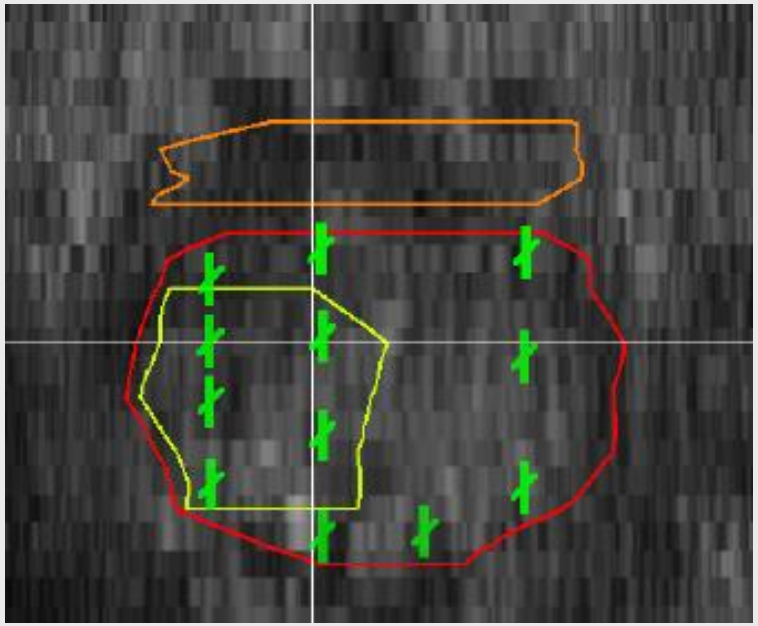
Baty, Cancer Radiothérapie 2019

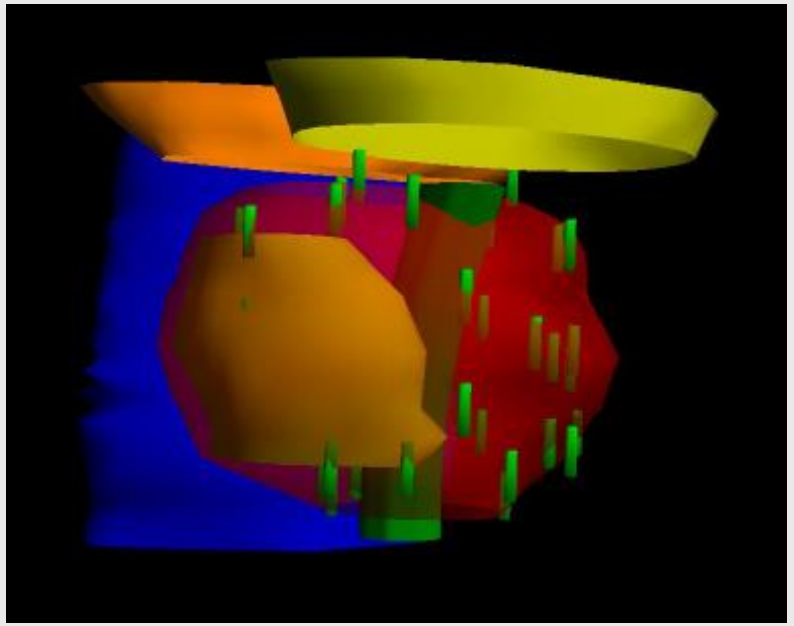
institut Curie

CAPRICUR

- Phase II prospective Française
- Patients séléctionnés ++
- Whole gland 90Gy en grains avec boost “intégré” sur la tumeur index IRM à 144Gy
- Avec spacer d’acide hyaluronique







Inclusions terminées, en attente des résultats

institut Curie

Conclusion

Curiethérapie de rattrapage : une autre arme dans l'arsenal thérapeutique

Semble moins toxique que la prostatectomie / cryo / HIFU de rattrapage

Plus de données que la stéréo

Sélection des patients ++

Technique rigoureuse

Category	Recommendations for salvage brachytherapy
Eligibility	Life expectancy >10 years, Able to tolerate anesthesia and procedure; Biopsy proven local recurrence, absence of distant metastases with standard restaging; PSMA PET if available; Initially LR or IR disease: pre-salvage PSA <10; PSADT >6 Mo, ≥3 years from EBRT (preferable >4.5 years); Minimal residual toxicity from prior EBRT (< grade 2)
Suggested constraints	LDR whole gland salvage (validated in RTOG 0526): ❖ ^{125}I: V150 ≤45%, V200 ≤10% ❖ ^{103}Pd V150 ≤55%, V200 ≤15% HDR whole gland (no validated constraints for single fraction or 2 fraction treatment): ❖ ^{192}Ir ❖ Two dose levels may be preferable ◆ 10 Gy to the whole gland ◆ Dose escalate DIL to 13.5 Gy ❖ Minimum 95% coverage with PD ❖ Maximum urethral dose ≤115% of PD ❖ Rectal D1cc <6 Gy, D0.1cc <85%

Tisseverasinghe and Crook. Transl Androl Urol 2018

institut Curie

Merci pour votre attention

Contact : manon.kissel@curie.fr

ENSEMBLE, PRENONS LE CANCER DE VITESSE

institut Curie