Radiothérapie stéréotaxique de novo

des cancers de la prostate

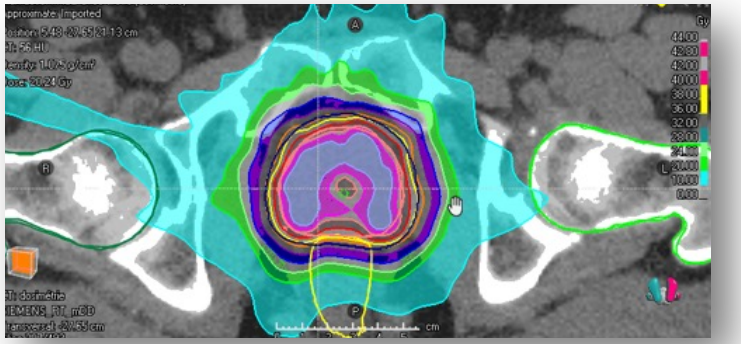
Pr D. PASQUIER

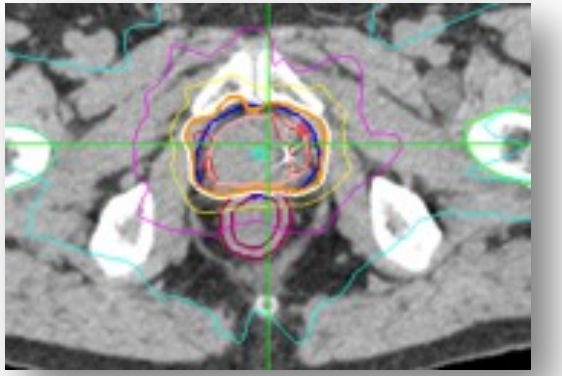
Université de Lille, Centre Oscar Lambret

Pôle de radiothérapie

CRIStAL UMR CNRS 9189

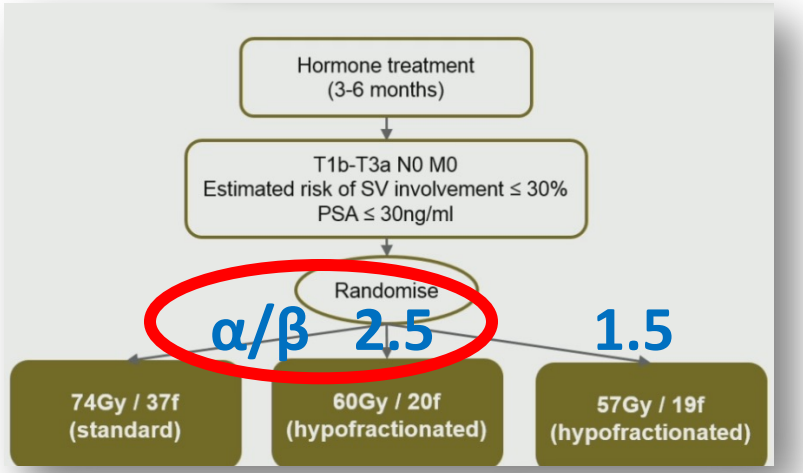
- Rationnel
- Essais randomisés
- Référentiels
- Contraintes pour les OAR
- IRM Linac
- Essais en cours

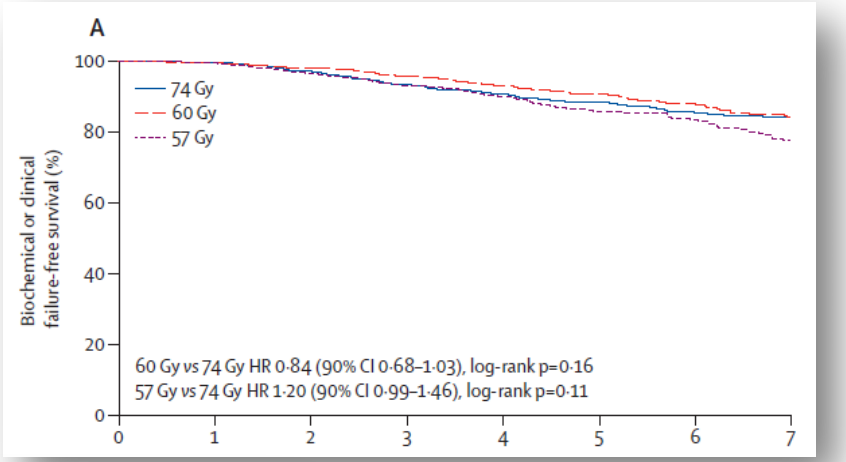


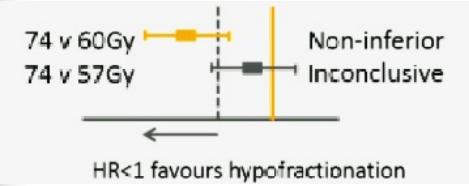


Valeur du rapport α/β ?

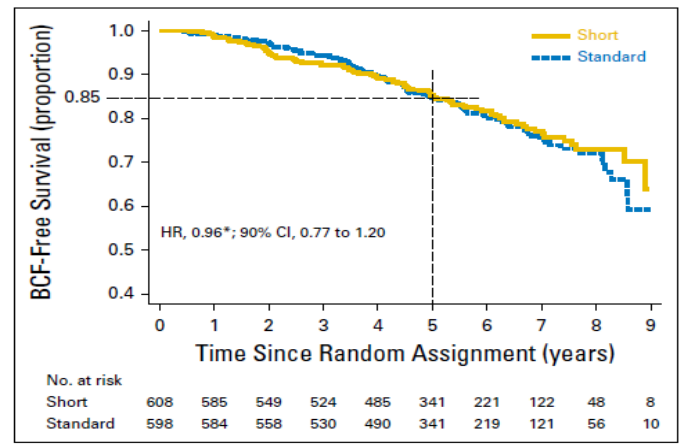
Hypofr. modéré: 20 x 3 Gy







78 Gy / 39 fr vs 60 Gy / 20 fr



Dearnaley Lancet Oncol 2016
Catton JCO 2017

2020’ Premiers essais randomisés !

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,

Patients and Method

- Open randomized phase III trial
  - Non-inferiority design
  - 1200 patients accrued
    - July 2005-Nov 2015
  - Intermediate risk PCa
    - T1c-T3a, PSA ≤ 20, Gl ≥7, 1-2 of these risk factors were required

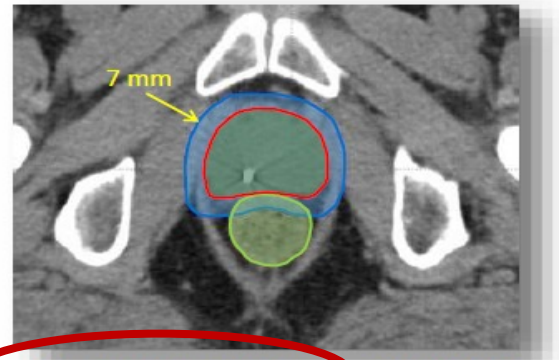
RANDOMIZE

Conventional fractionation (CF): 39*2.00 Gy = 78.0 Gy over 8 weeks

Extreme hypofractionation (E-HF): 7*6.10 Gy = 42.7 Gy over 2.5 weeks

PSA médian 8,6 ng/ml (IQR 6-12)

89 % RI (% RI « favor. » et « defav » ?)



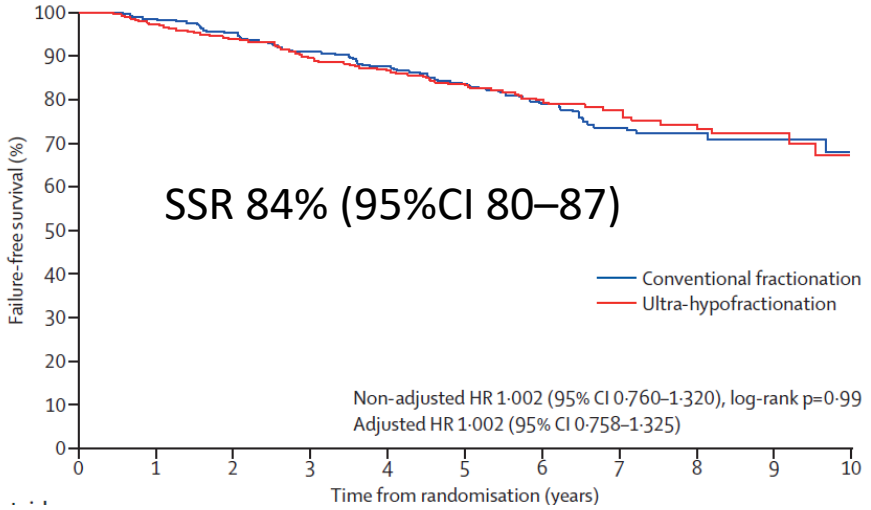
Hypofr. « extrême » sans RT stéréotaxique

Radiotherapy

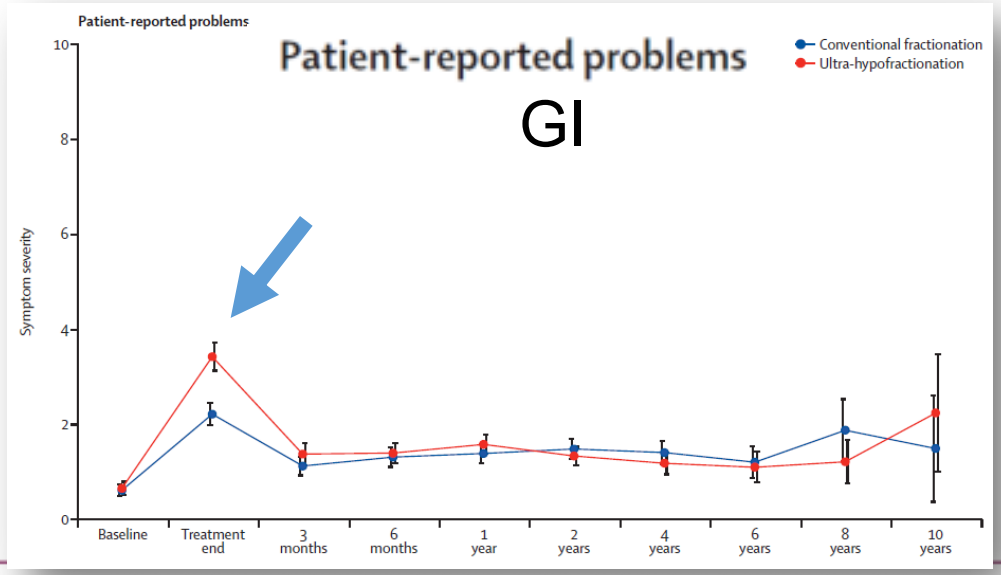
- IGRT
  - based on implanted markers
- CTV=prostate
  - no seminal vesicles
- PTV=CTV + 7 mm isotropic margin
- CTV delineated on CT
  - (with MR guidance)

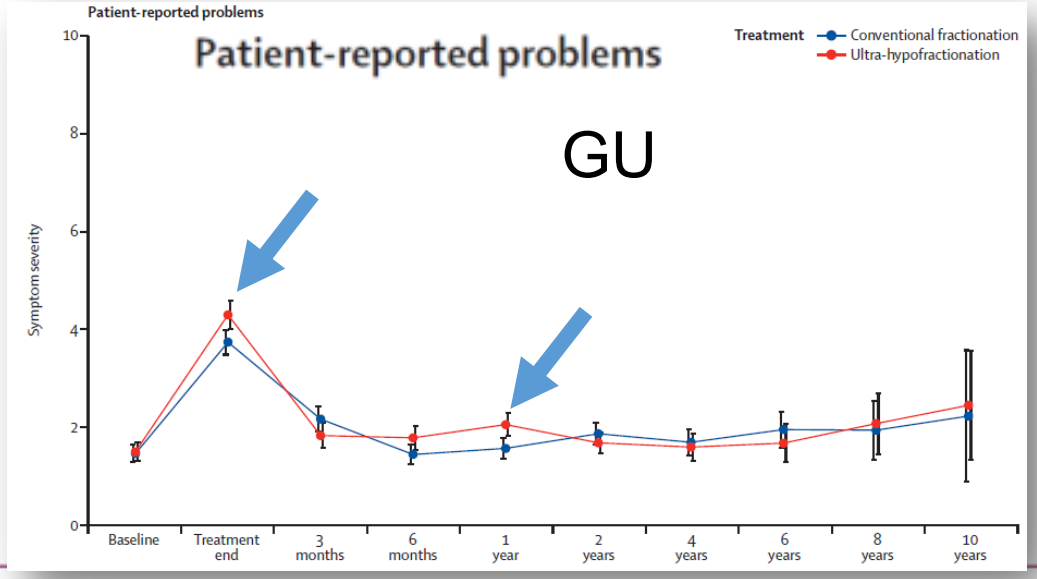
2020’ Premiers essais randomisés !

Suivi médian 5 ans (IQR 3-7)



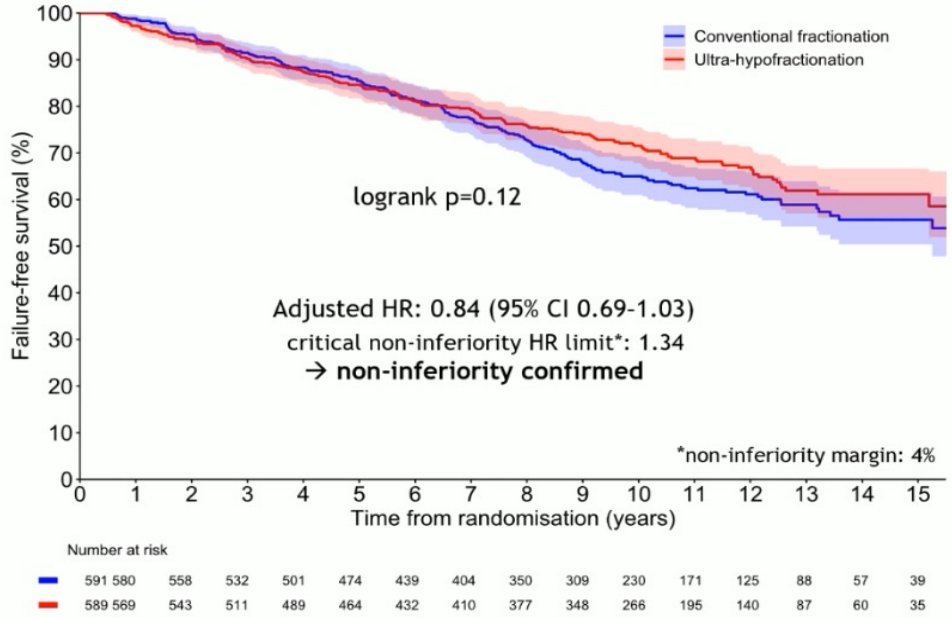
Tox. RTOG 5 ans	GI	GU
G2+	10% vs 10%	18% vs 17% p = 0,63



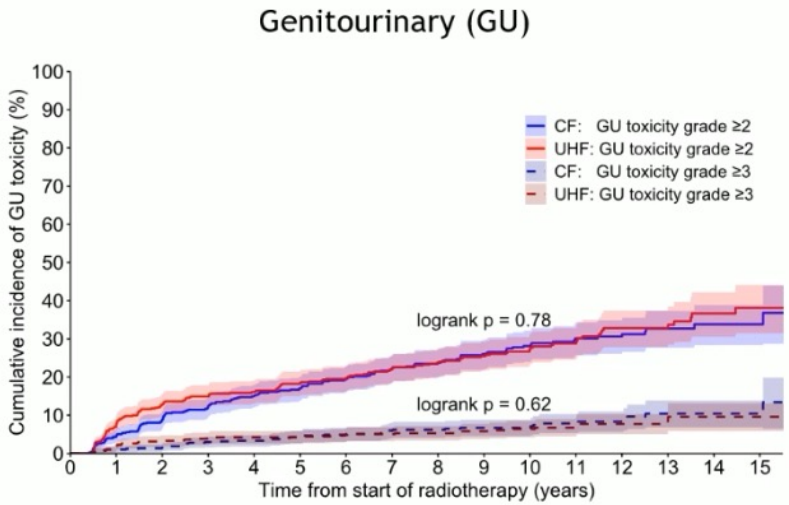


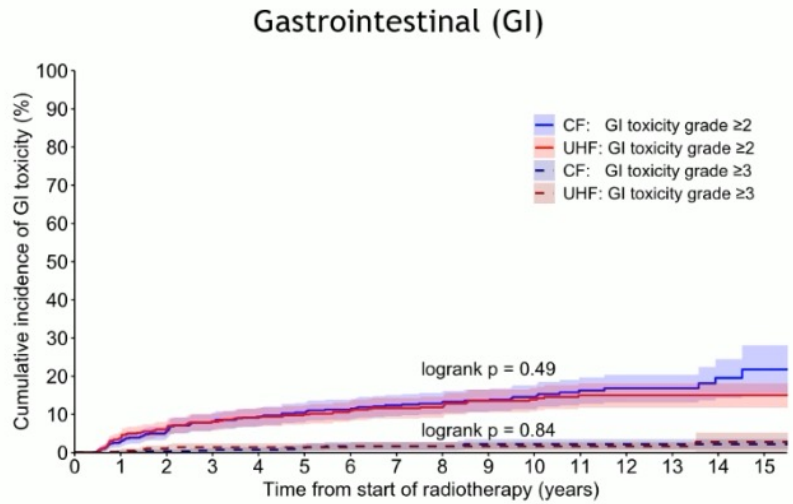
Primary endpoint — failure-free survival

- Median follow-up time
  10.6 years (IQR 9.1-12.9)
- Number of primary events
  UHF: 178
  CF: 205
- Failure-free survival at 10 years
  UHF: 72% (95% CI 68-76)
  CF: 65% (95% CI 61-69)



Late toxicity — cumulative incidence





The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of Stereotactic Body Radiotherapy in Localized Prostate Cancer

N. van As, C. Griffin, A. Tree, J. Patel, P. Ostler, H. van der Voet, A. Loblaw,

N Engl J Med 2024;391:1413-25.

Lancet Oncol 2022; 23: 1308–20

874 patients

2012-2018

Non infériorité SSR

8 % FR + **92 % RI** (Gleason **3+4**, **ISUP 2**)

- **RI favorable 24%**
- **RI défavorable 76%**

Prostate volume — no. (%)	
<40 ml	355 (40.6)
40 to <80 ml	421 (48.2)
≥80 ml	51 (5.8)
Unknown	47 (5.4)

International Prostate Symptom Score grade — no. (%)‖	
No symptoms: score of 0	37 (4.2)
Mild symptoms: score of 1–7	399 (45.7)
Moderate symptoms: score of 8–19	277 (31.7)
Severe symptoms: score of 20–35	43 (4.9)
Unknown	118 (13.5)

PSA médian 8 ng/ml (IQR 6-11)

5 x 7,25 Gy vs 39 x 2 Gy (ou 20 x 3,1 Gy)

RT stéréo: Linac 59% Cyberknife 41%

The PACE Trial

(Prostate Advances in Comparative Evidence)

International randomised study of laparoscopic prostatectomy vs stereotactic body radiotherapy (SBRT) and conventional radiotherapy vs SBRT for early stage organ-confined prostate cancer

PROTOCOL

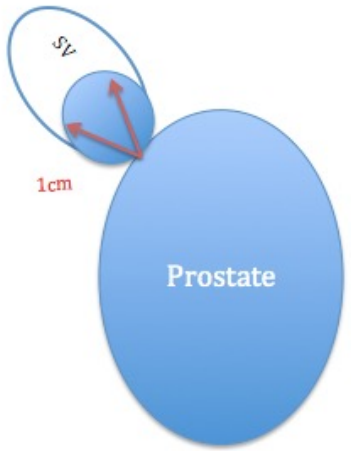
Version: 7.1

Dated: 24th March 2016

Fiduciels « hautement recommandés »

→ Recalage TDM IRM

All patients:
Low risk: CTV = prostate only (as defined on MRI planning scan where available)
Intermediate risk: CTV = prostate plus proximal 1cm of seminal vesicles from insertion point in the superior-inferior plane. This should include the middle ½ to ⅔ of seminal vesicle width (i.e. not the tips). Please contact the QA team for example contours.



Marges PTV	Toutes directions	Vers le rectum
Bras standard	5–9 mm	3–7 mm
RT stéréo	4–5 mm	3–5 mm

The prescription dose of 36.25 Gy shall be the dose to the PTV

CTV V40Gy > 95%

For gantry-based SBRT, the following dose objectives should be met with respect to the PTV: D98% ≥ 34.4 Gy, Dmax < 48 Gy, and aim for D2% ≤ 42.8 Gy, where possible

Cyberknife: isodose de prescription 65-85%
ou 75-85% si l'urètre n'est pas contouré

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

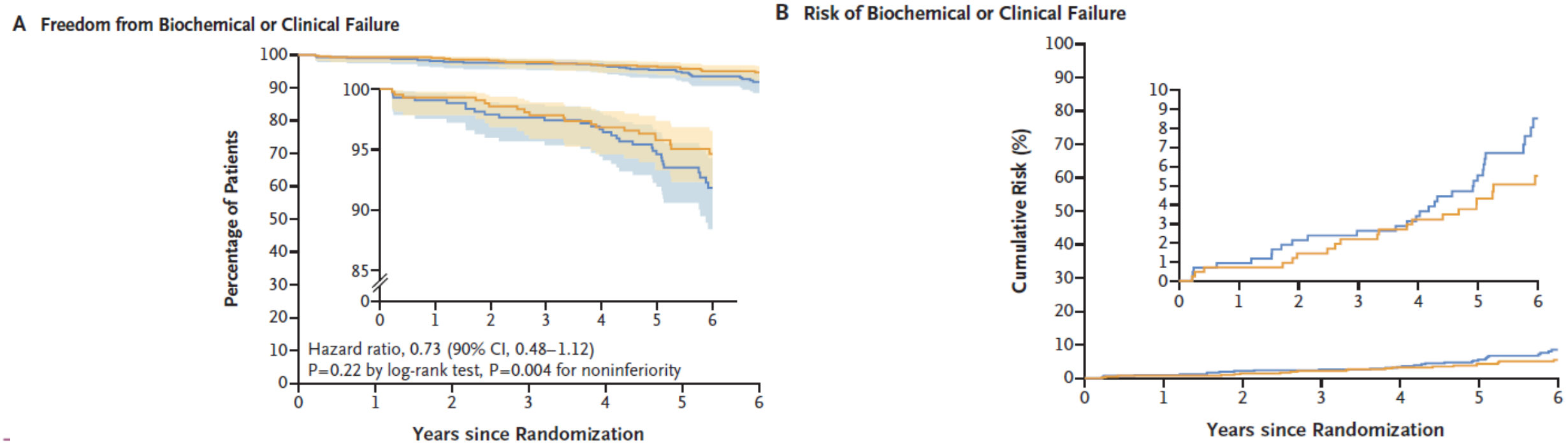
N Engl J Med 2024;391:1413-25.

Phase 3 Trial of Stereotactic Body Radiotherapy in Localized Prostate Cancer

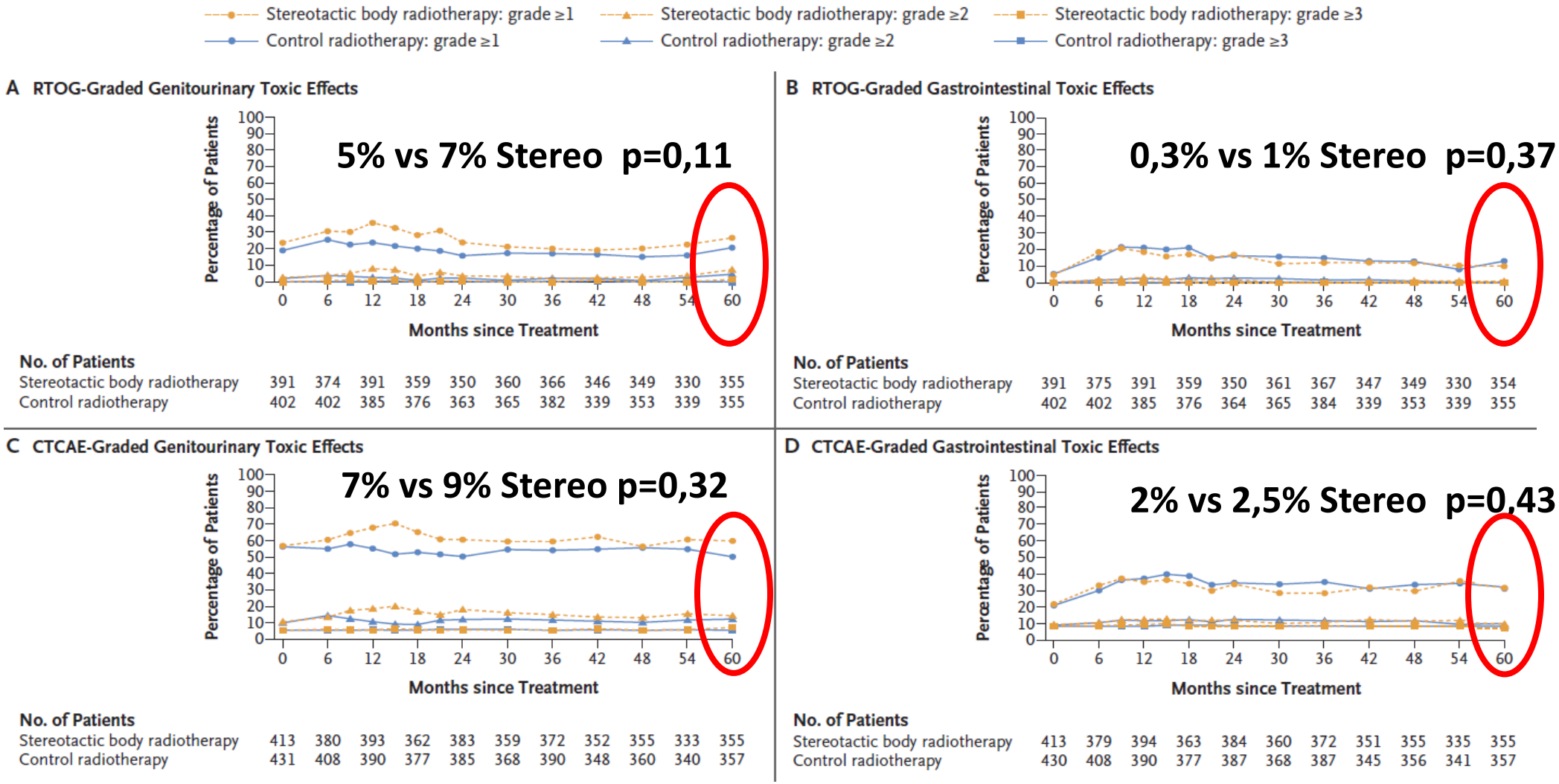
N. van As, C. Griffin, A. Tree, J. Patel, P. Ostler, H. van der Voet, A. Loblaw,

Suivi médian 74 mois

SSR à 5 ans 96% RT stéréo vs 95%



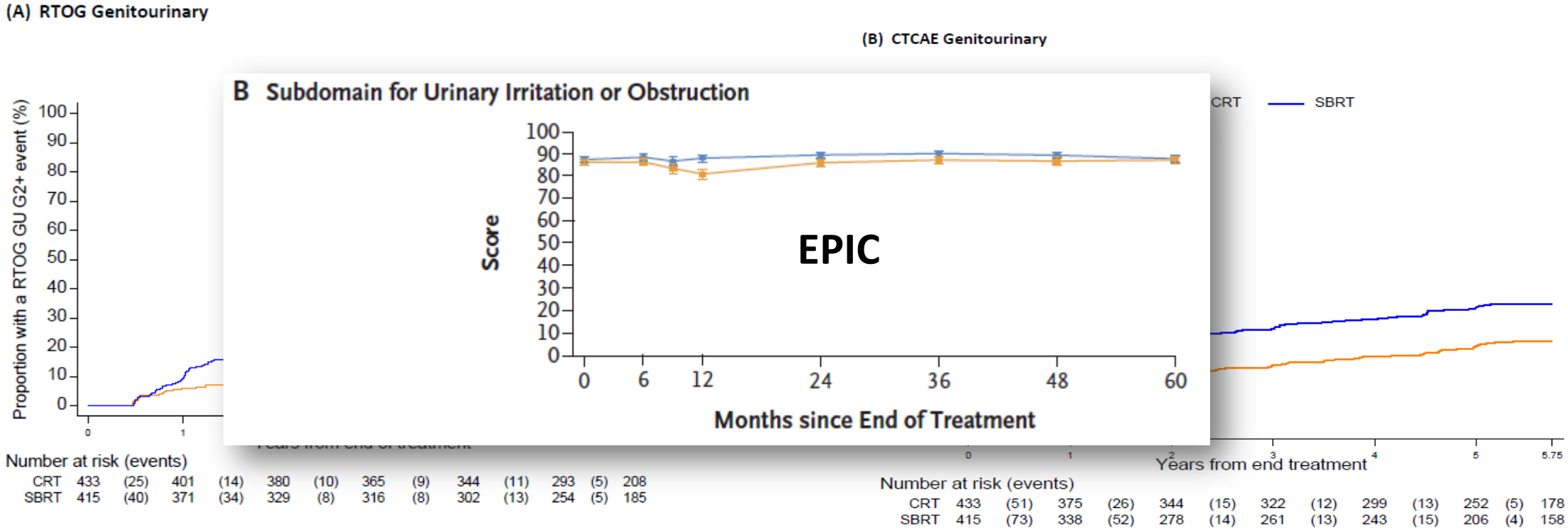
Toxicité G2+ GU et GI à 5 ans: NS



Incidence <u>cumulée</u> de toxicité GU G2+

18% (95%CI, 15-22) vs 27% (95%CI, 23-31)
(HR 1.59; 95%CI,1.18 - 2.12; p<0.001)

30% (95%CI, 25-34) vs 42% (95%CI,38-47)
(HR 1.58; 95%CI,1.25 - 2; p<0.001)

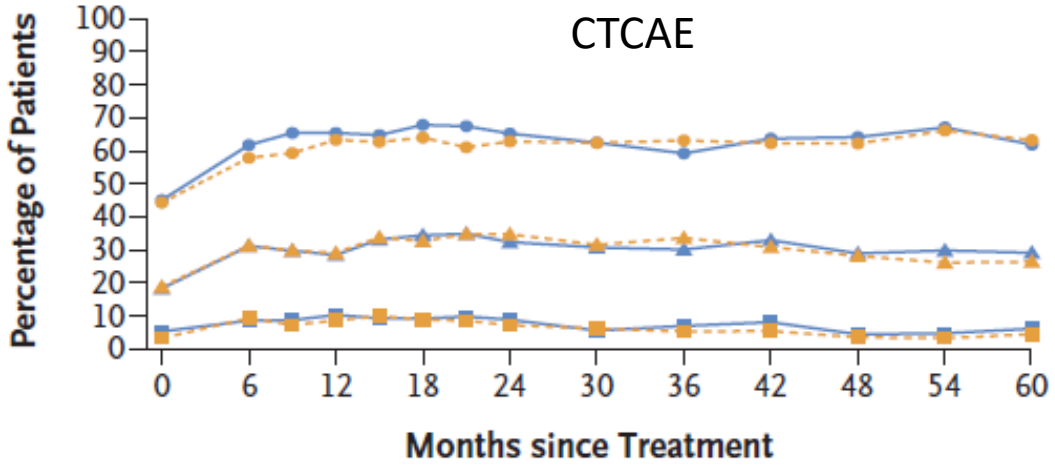


Incidence cumulée de toxicité GI G2+: NS

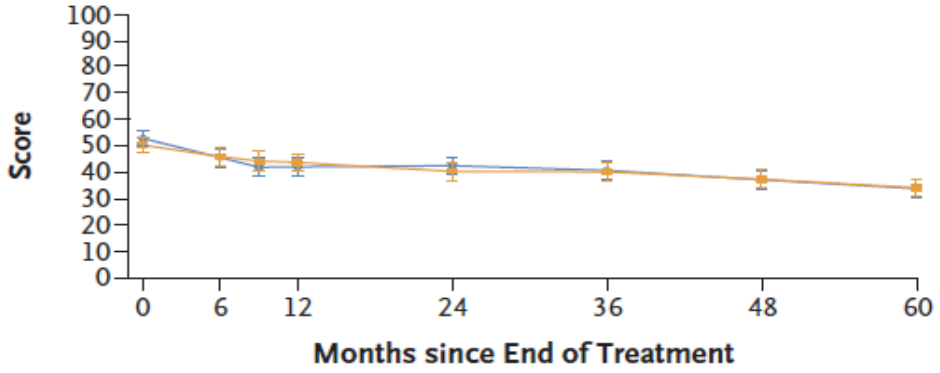
Fonction sexuelle

PACE-B

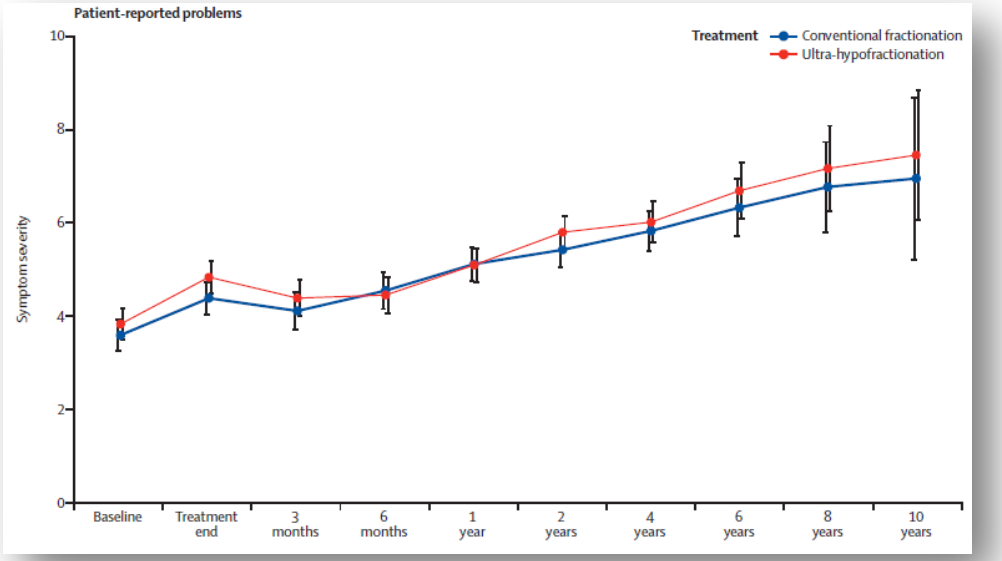
CTCAE



D Sexual Subdomain

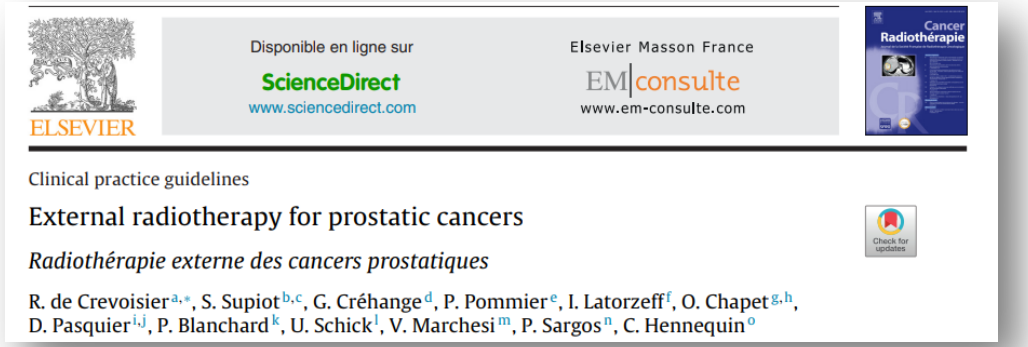


Hypo-RT-PC



Tree Lancet Oncol 2022, Van As NEJM 2024, Widmark Lancet 2019

Référentiels cancers de RI



Disponible en ligne sur ScienceDirect www.sciencedirect.com

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Cancer Radiothérapie

Clinical practice guidelines

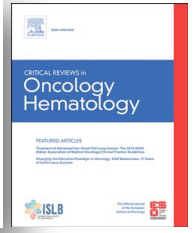
External radiotherapy for prostatic cancers

Radiothérapie externe des cancers prostatiques

R. de Crevoisier[a,*], S. Supiot[b,c], G. Créhange[d], P. Pommier[e], I. Latorzeff[f], O. Chapet[g,h], D. Pasquier[i,j], P. Blanchard[k], U. Schick[l], V. Marchesi[m], P. Sargos[n], C. Hennequin[o]

Recommended techniques	Acceptable techniques
Intermediate favorable risk	Daily prostate IMRT with IGRT Brachytherapy (iodine 125) SBRT : Extreme Hypofractionation
Intermediate risk Unfavorable risk	-Extreme hypofractionation: 35 to 40 Gy in 5 fr (36.25 Gy in 5 fr over 2 weeks)

Highly hypofractionated schedules for localized prostate cancer: Recommendations of the GETUG radiation oncology group 2022



Ariane Lapierre[a], Christophe Hennequin[b], Amandine Beneux[c], Sarah Belhomme[d], Nicolas Benziane Ouaritini[e], Marie-Claude Biston[f], Gilles Crehange[g], Renaud de Crevoisier[h], Jean-luc Dumas[i], Maher Fawzi[j], Albert Lisbona[k], David Pasquier[l], Sandra Pelissier[m], Pierre Graff-Cailleaud[n], Pascal Pommier[o], Paul Sargos[p], Jean-Marc Simon[q], Stéphane Supiot[r], Florence Tantot[s], Olivier Chapet[t,*]

In conclusion, patients in the intermediate favorable prognostic group are the best candidates for a SBRT regimen.

IPSS ≤ 15
Volume prostate ≤ 80 cc
Si RTUP: > 3 mois avant RTS

Recommandations françaises du comité de cancérologie de l'AFU – Actualisation 2024–2026 : cancer de la prostate – diagnostic et prise en charge de la maladie localisée☆

Radiothérapie stéréotaxique - seule si intermédiaire favorable - ou associée à une hormonothérapie courte (6 mois) si risque intermédiaire défavorable	Faible

EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on

Prostate Cancer

P. Cornford (Chair), D. Tilki (Vice-chair), R.C.N. van den Bergh,

*Guidelines for the treatment of intermediate-risk disease**

Radiotherapeutic treatment	
Offer intensity-modulated radiotherapy (IMRT)/volumetric modulated arc therapy (VMAT) plus image-guided radiotherapy (IGRT), with a total dose of 76–78 Gy or moderate hypofractionation (60 Gy/20 fx in 4 weeks or 70 Gy/28 fx in 6 weeks), in combination with short-term androgen deprivation therapy (ADT) (four to six months).	Strong
Offer ultra-hypofractionated IMRT/IGRT or SBRT, using either 36.25 Gy (40 Gy to prostate) in 5 fx or 42.7 Gy in 7 fx delivered alternate days.	Weak

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2024
Prostate Cancer

Regimen	Preferred Dose/Fractionation	NCCN Risk Group (✓ indicates an appropriate regimen option if RT is given)				
		Very Low and Low	Favorable Intermediate	Unfavorable Intermediate	High and Very High	Regional N1[e]
SBRT Ultra-Hypofractionation	9.5 Gy x 4 fx 7.25–8 Gy x 5 fx[c] 6.1 Gy x 7 fx[c]	✓	✓	✓	✓ ? ?	

Contraintes pour les OAR

Contraintes de l'essai PACE-B

Rectum et vessie:
organes « pleins » (pas les parois)

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

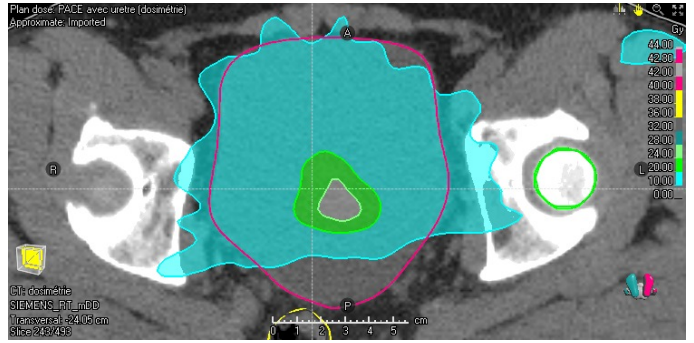
UK 2022 Consensus on Normal Tissue Dose-Volume Constraints for Oligometastatic, Primary Lung and Hepatocellular Carcinoma Stereotactic Ablative Radiotherapy

P. Diez *, G.G. Hanna †‡, K.L. Aitken §¶, N. van As ¶‖, A. Carver **, R.J. Colaco ††, J. Conibear ‡‡,

Description	Constraint (prostate primary only)	5 fractions		Source
		Optimal	Mandatory	
Rectum	D50%	–	<18.1 Gy	PACE trial [12]
	D20%	–	<29 Gy	
	D1 cm^3	–	<36 Gy	
Bladder	D40%	–	<18.1 Gy	As above
	V37 Gy	<5 cm^3	<10 cm^3	
Prostatic urethra (if visible)	D50%	<42 Gy	–	As above
Femoral head	D5%	–	<14.5 Gy	As above
Penile bulb	D50%	–	<29.5 Gy	As above
Testicles	Avoid beam entry, e.g. blocking structure			As above
Bowel	D5 cm^3	–	<18.1 Gy	As above
	D1 cm^3	–	<30 Gy	

D5%, D20%, D40% and D50% are the minimum doses to the percentage volume of the organ (5%, 20%, etc.) that receive the highest doses. D50% is equivalent to the median dose to the volume.
D1 cm^3 and D5 cm^3 are the minimum doses to the specified volume of the organ (1 cm^3, 5 cm^3) that receive the highest doses.
V37 Gy is the absolute volume of the organ receiving a dose of 37 Gy or higher.

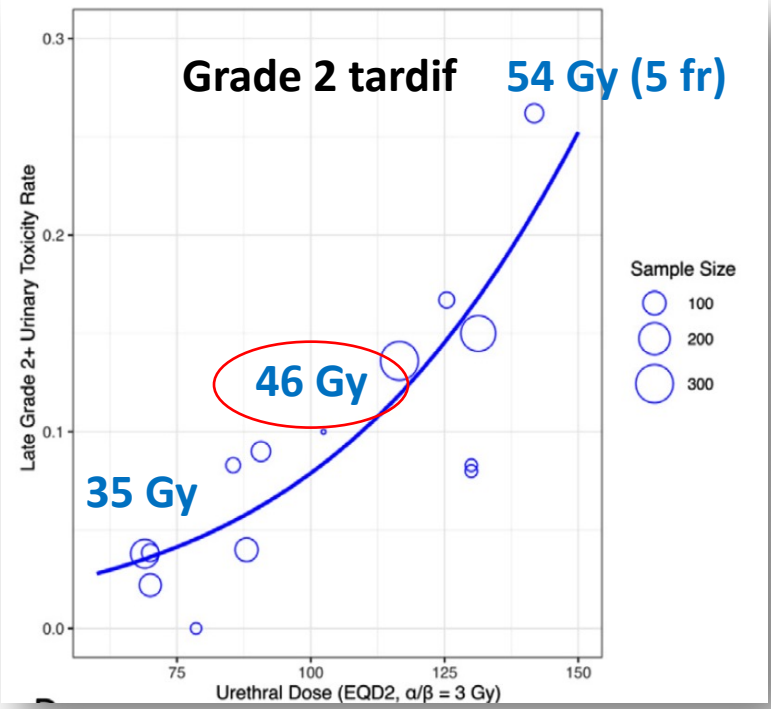
L’urètre, un « nouvel » OAR !

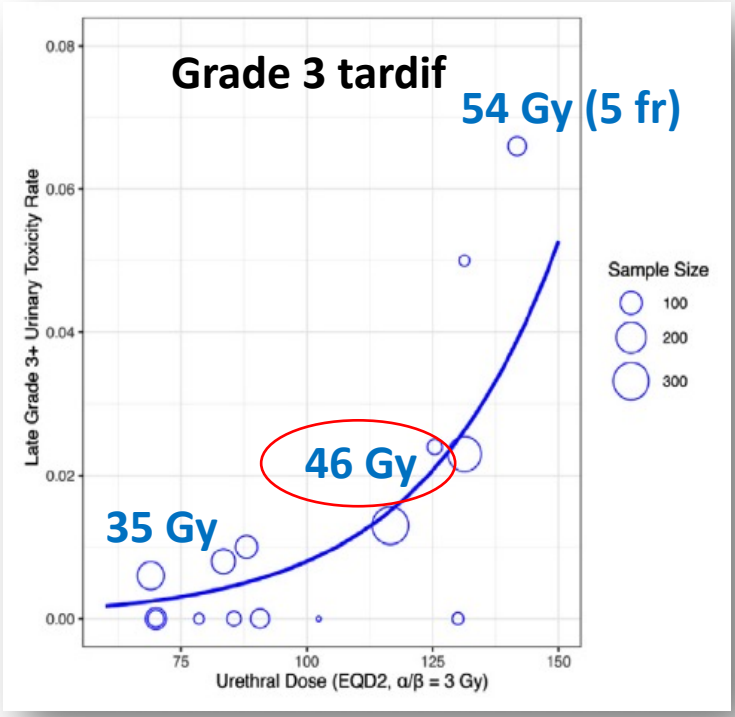


2200 patients; séries prospectives **Dmax urètre** (4-5 fractions)

Dmax urètre associée tox. GU aigüe et tardive G2+ (p<0,05); plus “robuste” que la dose prescrite !

5 fractions:
+ 1 Gy
→ + 1% G2 tardif





Leeman IJROBP 2022

Quelles marges de PTV ?

Dépend des techniques: fiduciels, gating, tracking,…

HYPO RT PC (sans technique stéréo): 7 mm !

PACEs A-C: 4-5 mm, sauf 3-5 mm vers le rectum (fiduciels « fortement recommandés »)

→ Attention aux marges très « faibles » ?

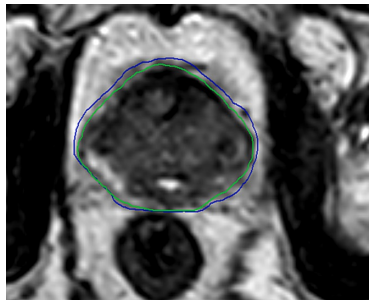
Prostate volume variation during 1.5T MR-guided adaptive stereotactic body radiotherapy (SBRT) and correlation with treatment toxicity

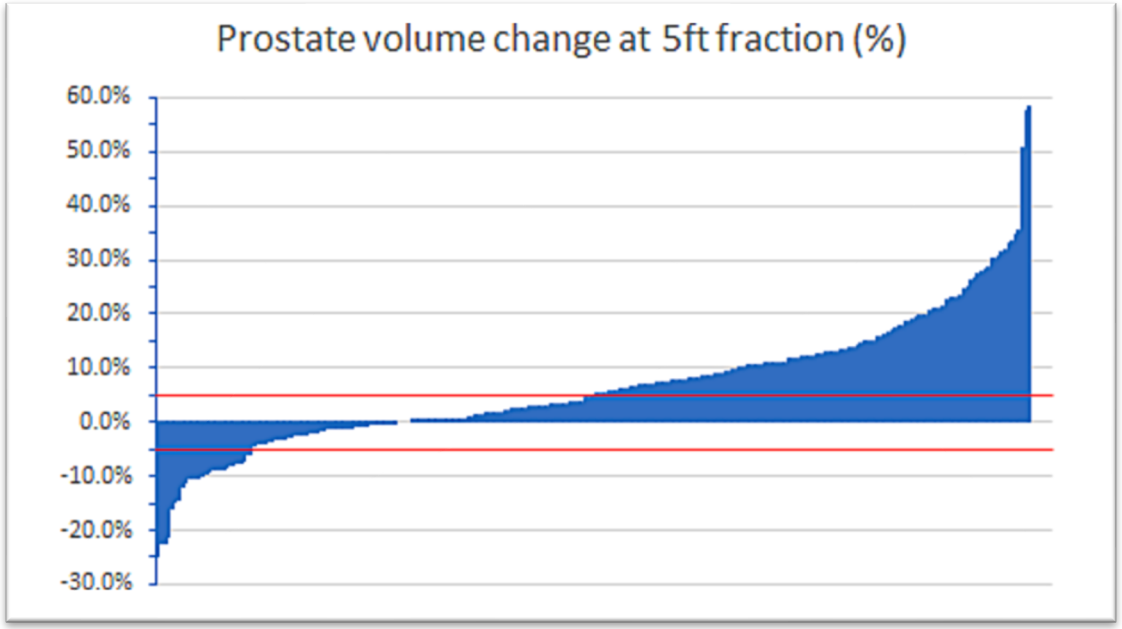
Luca Nicosia [a,*], Paolo Ravelli [a], Michele Rigo [a], Niccolò Giaj-Levra [a], Rosario Mazzola [a], Edoardo Pastorello [a], Francesco Ricchetti [a], Andrea Gaetano Allegra [a], Ruggero Ruggieri [a], Filippo Alongi [a,b]

2024

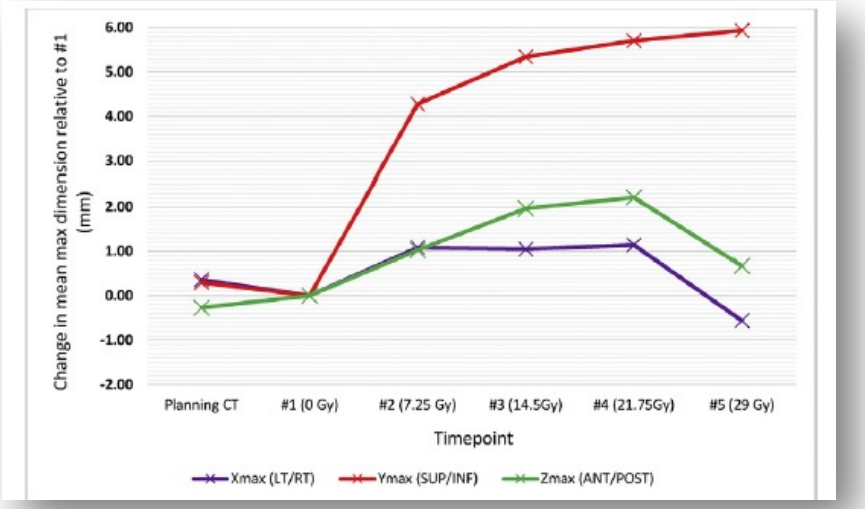
N = 254 5 x 7,25 Gy

Majoration moyenne 15% (5-58%)





Majoration maximale 4 - 6 mm séances 2 à 5
Axe supéro inferieur +++



Alexander Clin Oncol 2022

IRM Linac

Essai de phase III

JAMA Oncology | Original Investigation

Magnetic Resonance Imaging–Guided vs Computed Tomography–Guided Stereotactic Body Radiotherapy for Prostate Cancer

The MIRAGE Randomized Clinical Trial 2023

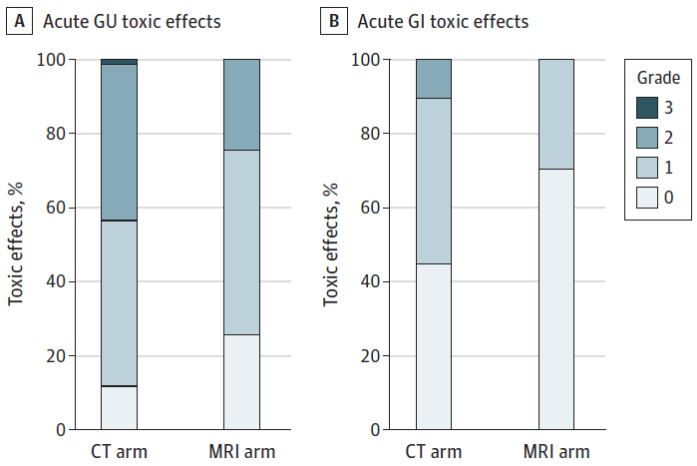
Amar U. Kishan, MD; Ting Martin Ma, MD, PhD; James M. Lamb, PhD; Maria Casado, BS; Holly Wilhalme, MSc; Daniel A. Low, PhD; Ke Sheng, PhD; Sahil Sharma, BS; Nicholas G. Nickols, MD, PhD; Jonathan Pham, PhD; Yingli Yang, PhD; Yu Gao, PhD; John Neylon, PhD; Vincent Basehart, BS; Minsong Cao, PhD; Michael L. Steinberg, MD

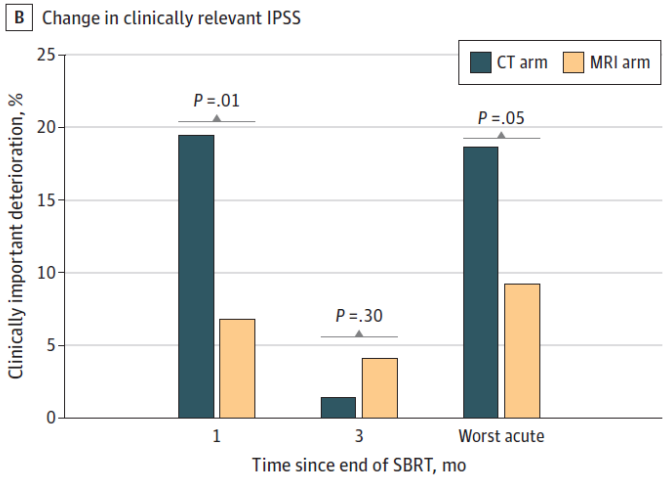
5 x 8 Gy 178 patients RT stéréo guidée par CBCT vs IRM

Marges 4mm (CBCT) vs 2mm (MRI) Obj principal= tox. aigüe grade 2+ GU

Tox. grade 2+ GU 24.4% vs 43.4%; $p = 0.01$

Tox. grade 2+ GI 0.0% vs 10.5%; $p = 0.003$





Place de l'IRM Linac

Essai de phase III

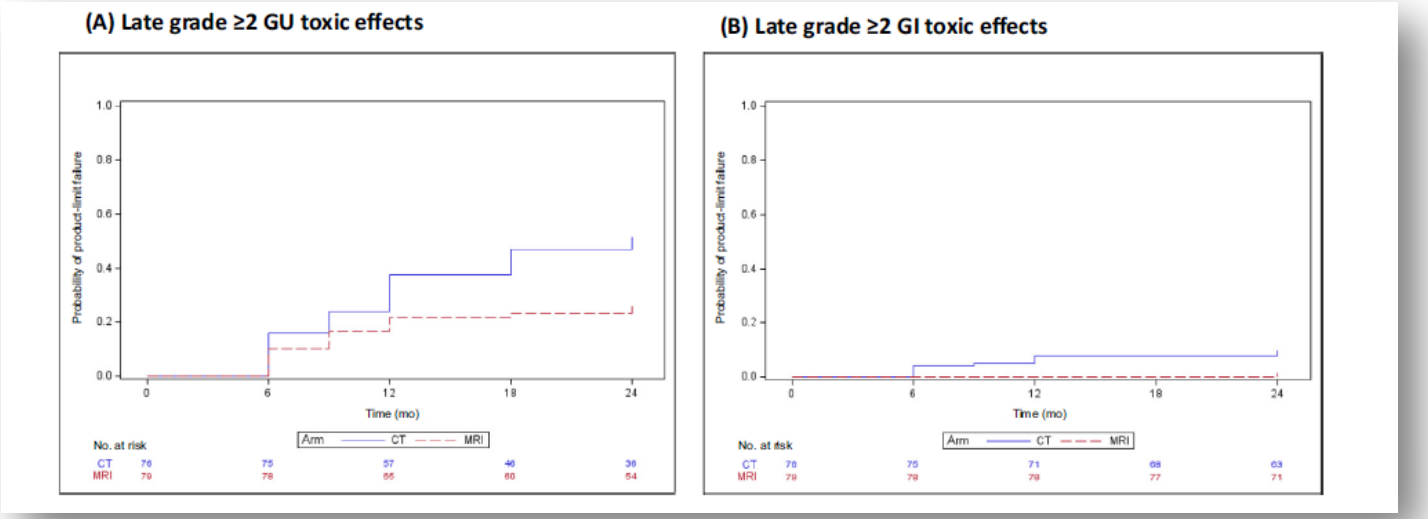
Magnetic Resonance Imaging Versus Computed Tomography Guidance for Stereotactic Body Radiotherapy in Prostate Cancer: 2-year Outcomes from the MIRAGE Randomized Clinical Trial

2024

Amar U. Kishan [a,b,], James M. Lamb [a], Holly Wilhalme [c], Maria Casado [a], Natalie Chong [a], Lily Zello [a],*

Tox. grade 2+ GU 27% vs 51% p = 0.004

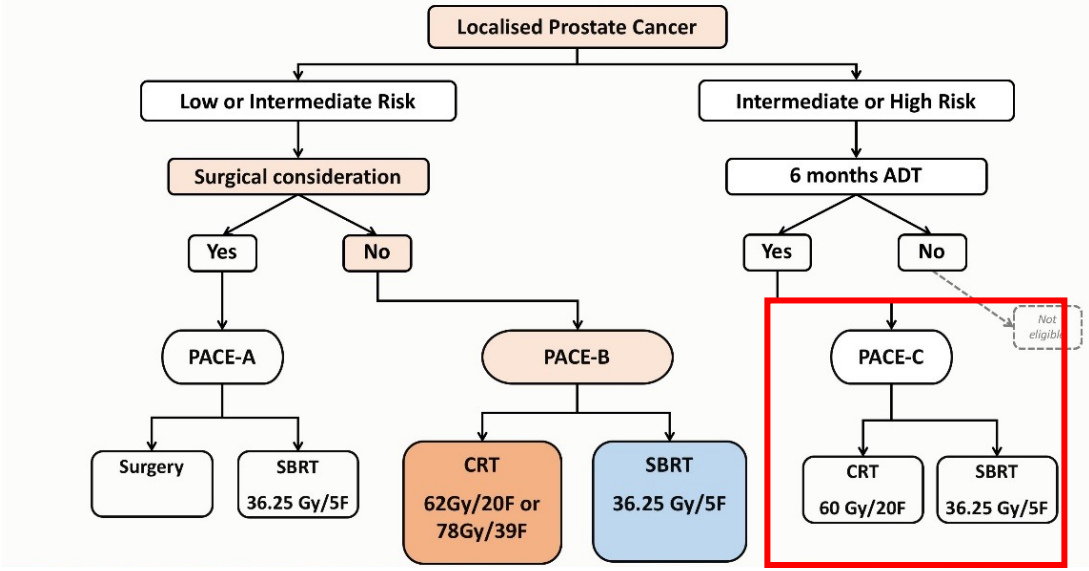
Tox. grade 2+ GI 1.4% vs 9.5% p = 0.025



Outcome	Odds ratio (95% CI)	*p* value
EPIC-26 urinary incontinence	0.72 (0.31–1.68)	0.4
EPIC-26 urinary irritative symptoms	0.54 (0.25–1.17)	0.12
EPIC-26 bowel function	0.44 (0.21–0.94)	**0.035**
EPIC-26 sexual function	0.68 (0.27–1.69)	0.4
International Prostate Symptom Score	0.71 (0.23–2.15)	0.5
Sexual Health Inventory for Men	0.37 (0.15–0.91)	**0.03**

EPIC-26 = Expanded Prostate Cancer Index Composite-26; CI = confidence interval.

Essais en cours



Cancers à haut risque de récidive

PACE-C RI et HR

Phase III 60 Gy en 20 vs 36.25 Gy en 5 séances (HT 6-12 mois)

Obj. principal = SSR; n = 1182 Données tox aigues publiées (Tree Lancet Oncol 2025)

PACE-NODES Phase III 36.25 Gy en 5 séances ± RT pelvienne 25 Gy en 5 séances (HT 12-36 mois)

Obj. principal = SSR

n = 536 2022 –

HYPO FLAME 3.0 Phases III 62 Gy en 20 fr. vs 5 x 7 Gy + boost GTV 50 Gy

Obj principal = SSR (supériorité) n = 484

Essais en cours

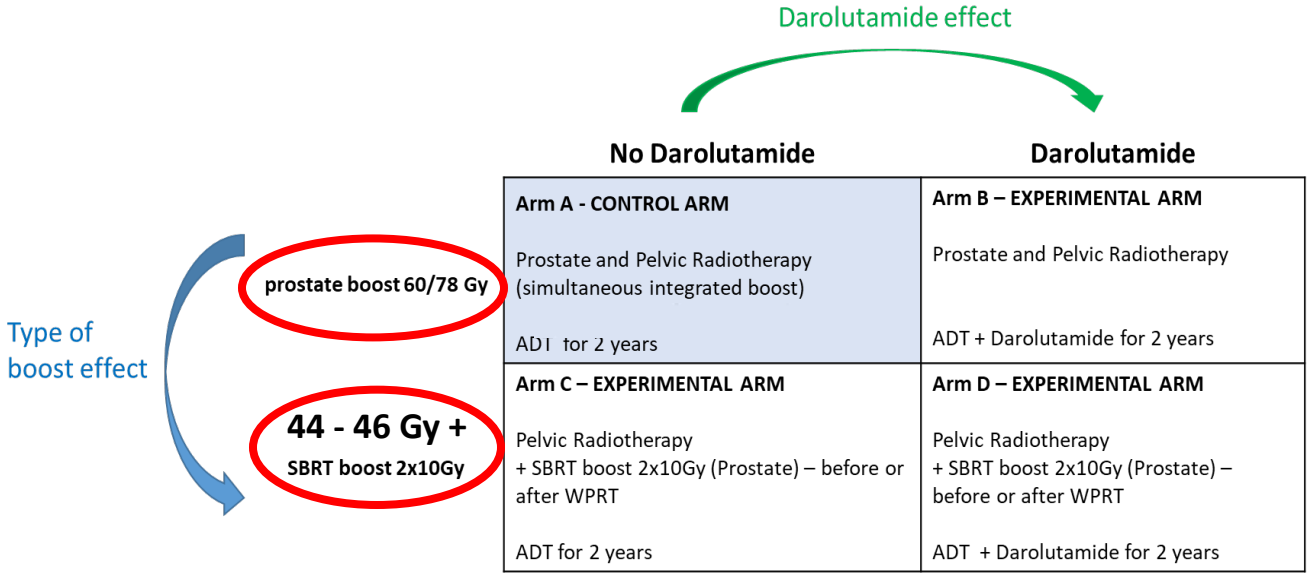
PEACE 7 (≥ 2 critères Ht Risque)

Phase III Plan factoriel 2 x 2

Boost glande entière et Daro.

Obj. principal = SS métastases

n = 700 2025 -



ORION Etude médico-économique de phase III

5 x 7,25 Gy + boost jusqu'à 50 Gy + RT pelvienne 5 x 5 Gy **vs** 39 x 2 Gy + RT pelvienne

n = 300

Conclusion

Progrès techniques → hypofr. modéré puis « extrême »

2 essais randomisés → option → ***standard*** pour cancer RI

Sélection des patients (volume, IPSS,…)

Attention au mode de prescription, dose à l'urètre

Places - du boost au GTV

- dans le cancer à haut risque à déterminer