Stratégies thérapeutique dans les cancers de prostate N+

Stéphane Supiot,

Oncologie Radiothérapie, ICO Nantes

Lien d’intérêt

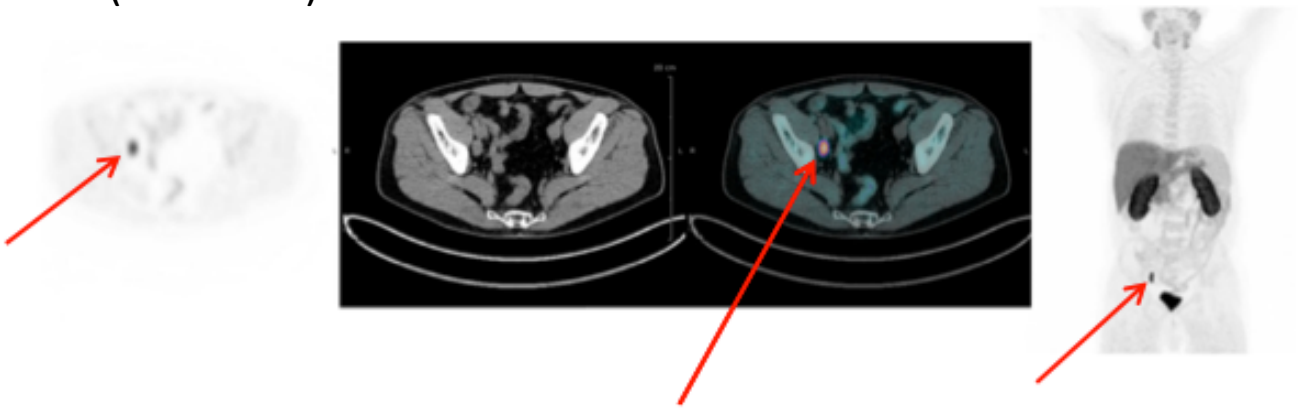
- Aucun en rapport avec ce sujet

Définition cancer de prostate N1: une entité rare ?

12 % des 50 000 cancers de prostate détectés chaque année = 6000 cas/an

- TDM abdomen pelvis : adp > 10 mm ? 15 mm ?
- IRM abdomen pelvis
- Curage ganglionnaire avortés = cN1 ?

- TEP FCH (+PSMA …)



http://seer.cancer.gov/statfacts/html/prost.html

Distinction

cN1

- TDM le plus souvent
- TEP ? IRM ?

pN1

- Curage ganglionnaire
- +/- extensif
- +/- prostatectomie

Patients cN1 :

Patients cN1 :
pas de preuves de niveau 1 de l'utilité de la chirurgie ou 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

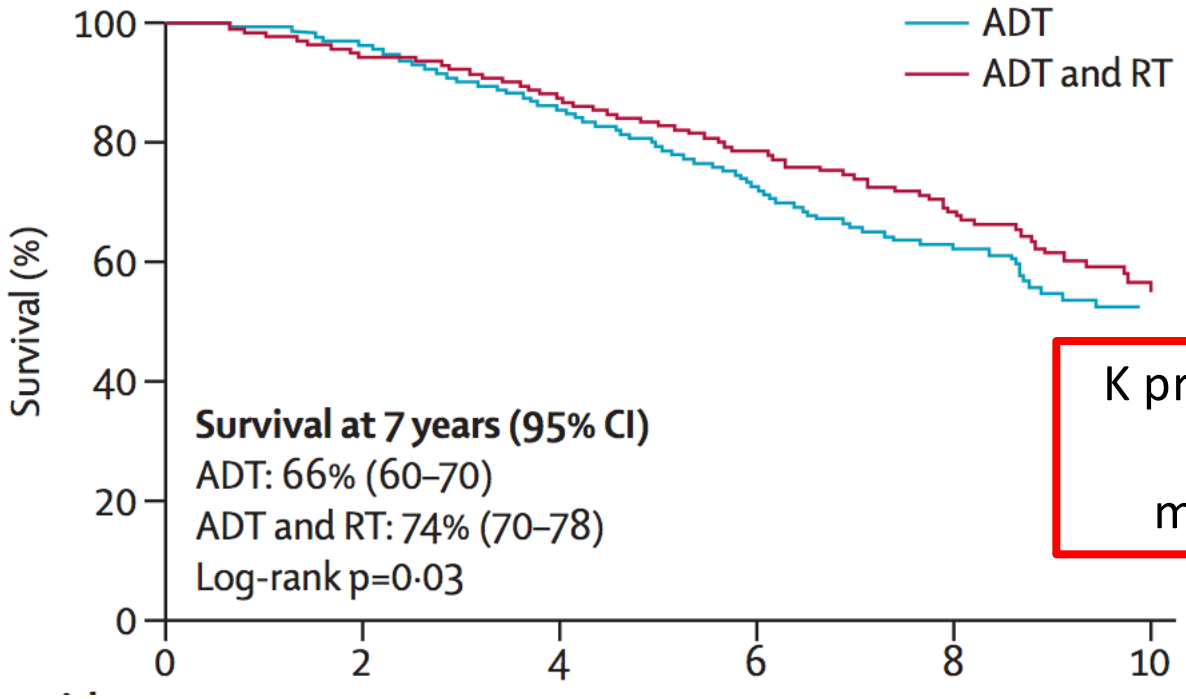
	Protocole	SG (%) 8-10 ans
D'Amico, JAMA. 2008	RT +/- HT 6 mois	74 *vs* 61 s
Roach, JCO 2008	RT +/- HT 4 mois	43 *vs* 34 ns
Bolla, Lancet Onc 2010	RT +/- HT 3 ans	58 *vs* 39 s

HT +RT > HT seule

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

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

OR : études faites à époque où imagerie moins précise
Rôle RT si N+ d'emblée ?

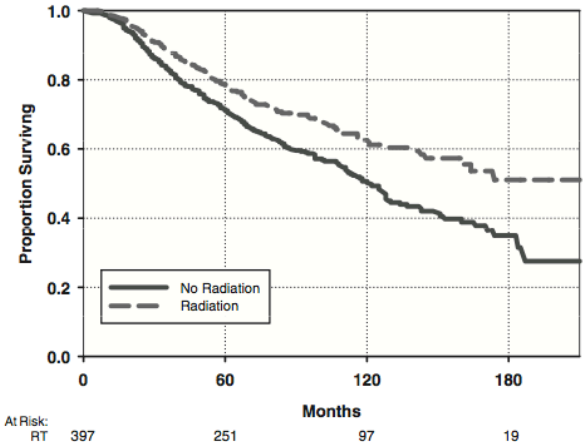


K prostate de haut risque
= Maladie
micrométastatique ?

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

Données de registre

Données SEER 1988-2006
1100 patients
RT = meilleure survie spécifique à 10 ans (63 % vs 50%, p<0,01)



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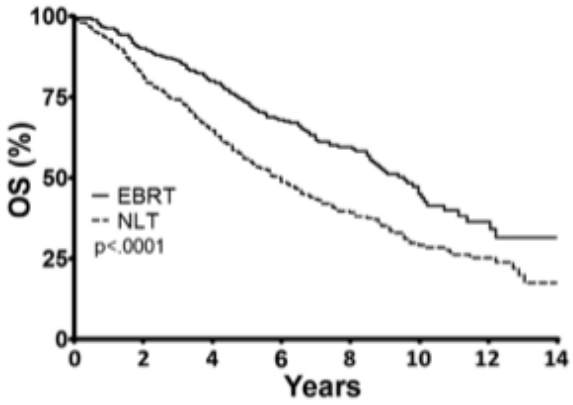
Données SEER 1995-2005
patients cN1
869 patients



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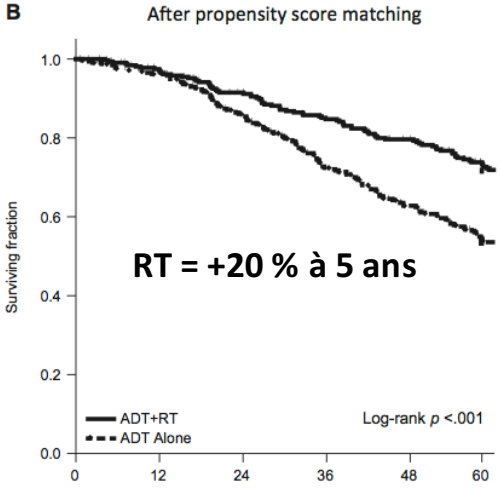
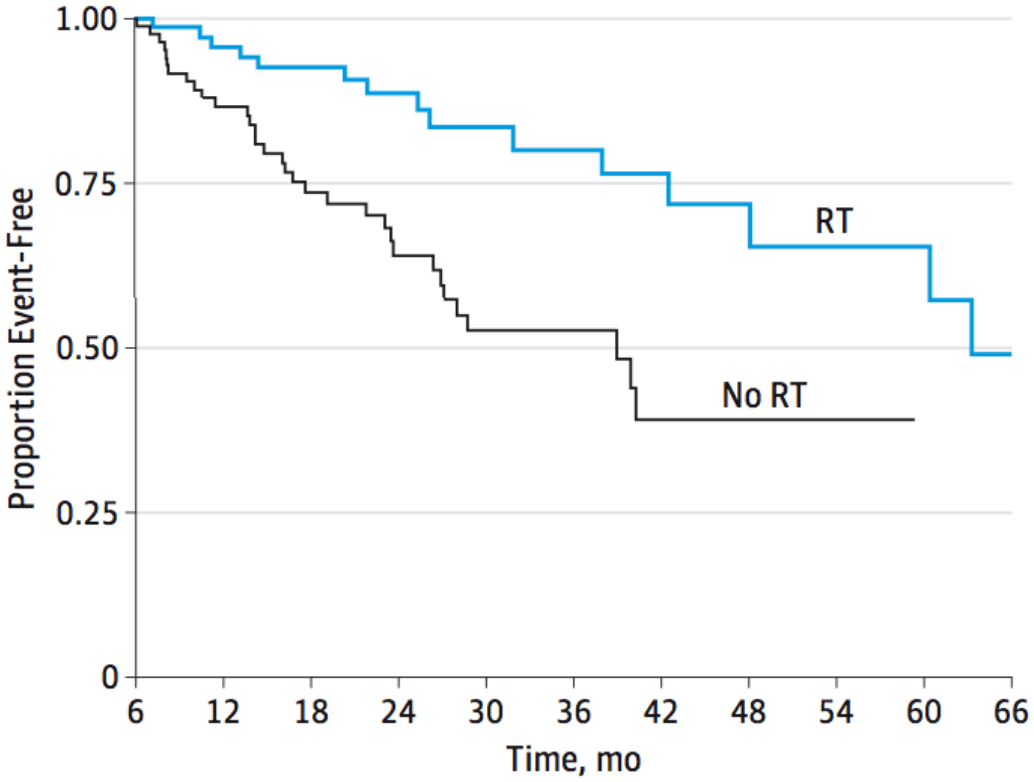
Données National Cancer Data Base (NCI)
636 patients
survie à 5 ans dans le groupe irradié (72% contre 53%, p<0,001)



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

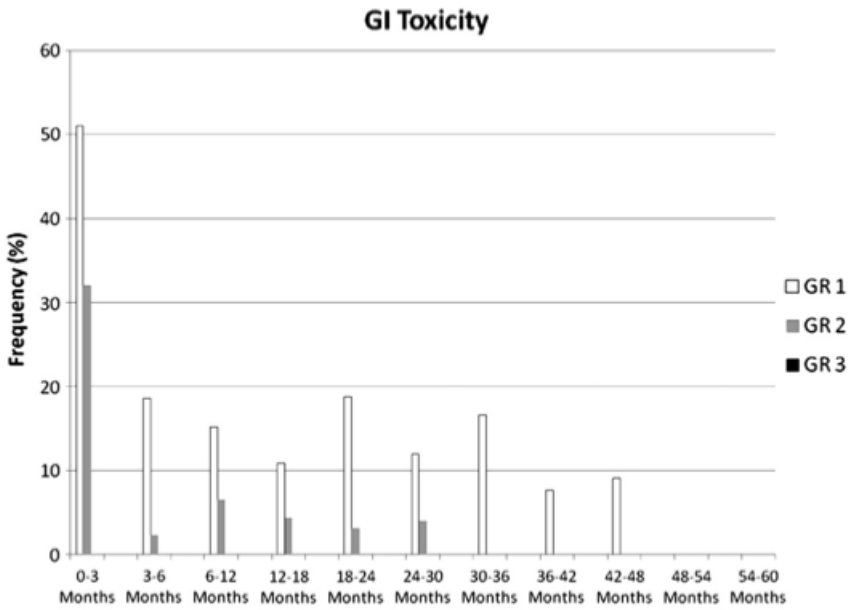
James et al. Failure-Free Survival and Radiotherapy in Patients With Newly Diagnosed Nonmetastatic Prostate Cancer: Data From Patients in the Control Arm of the STAMPEDE Trial. JAMA Oncol (2015) pp. 1-10

Quelle est la toxicité digestive de RT ganglionnaire ?

- Sans RCMI : toxicité aiguë +++
- Avec RCMI : peu de toxicité, même avec fortes doses (ex : 56 Gy, 28 f / 55,1 Gy, 29f)

Table 2. Radiation Therapy Oncology Group (RTOG) acute toxicity scores for current protocol

RTOG grade	Genitou rinary *n*	Genitou rinary %	Gastroin testinal *n*	Gastroin testinal %
0	5	4.9%	22	21.4%
1	50	48.5%	47	45.6%
2	45	43.7%	32	31.1%
3	3	2.9%	2	1.9%



- Bayley et al. Clinical application of high-dose, image-guided intensity-modulated radiotherapy in high-risk prostate cancer. Int J Radiat Oncol Biol Phys (2010) vol. 77 (2) pp. 477-83
- Adkison et al. Phase I Trial of Pelvic Nodal Dose Escalation With Hypofractionated IMRT for High-Risk Prostate Cancer. Int J Radiat Oncol Biol Phys (2012) vol. 82 (1) pp. 184-90

En pratique…

Table 2 Primary Treatment for Clinically Node-Positive Prostate Cancer Patients Within 1 Year of Diagnosis

Year	Prostatectomy	RT With ADT	RT Alone	ADT Alone	No Tx/Other[a]
2006	90 (8.3)	319 (29.2)	34 (3.1)	478 (43.8)	171 (15.7)
2007	91 (7.9)	328 (28.6)	40 (3.5)	492 (42.9)	195 (17.0)
2008	118 (8.8)	369 (27.5)	54 (4.0)	596 (44.5)	203 (15.2)
2009	149 (9.6)	413 (26.7)	59 (3.8)	726 (46.9)	201 (13.0)
2010	160 (9.8)	455 (27.9)	47 (2.9)	778 (47.7)	192 (11.8)
2011	114 (6.7)	488 (28.6)	51 (3.0)	822 (48.2)	231 (13.5)
Total	722 (8.5)	2372 (28.0)	285 (3.4)	3892 (46.0)	1193 (14.1)

Moon, D. H., Basak, R. S. & Chen, R. C. Patterns of Care of Node-Positive Prostate Cancer Patients Across the United States: A National Cancer Data Base Analysis. *Clinical Genitourinary Cancer* (2017). doi:10.1016/j.clgc.2017.08.004

Invited Commentary

Pelvis Plus Prostate Radiation Therapy and the Risk of Death in Men With Newly Diagnosed Node-Positive Prostate Cancer

Anthony V. D'Amico, MD, PhD

Both single-institutional retrospective series and a multi-institutional observational study[1,2] find a significant association between a reduced risk of death and treatment of node-positive prostate cancer using both external-beam radiation treatment (EBRT) of the prostate and pelvic lymph nodes (LNs) and androgen deprivation therapy (ADT) compared with ADT alone. However, whether this association is causal remains unanswered and requires testing in a prospective randomized trial. In this issue of *JAMA Oncology*, James and colleagues[3] use data from the control arm in the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) Trial to investigate this issue.

Related article page 348

Specifically, they perform a Cox regression multivariable analysis[4] evaluating the risk of failure-free survival where failure is defined as prostate-specific antigen (PSA) level; local, related failure events at this short median follow-up time make it difficult to predict what effect a reduction in mostly PSA failure-free survival will have on overall survival. Moreover, given the low event rate (20 of 177 [11.3%]), the authors were not able to analyze overall survival as an end point or adjust for all known prostate cancer prognostic factors in their model, such as tumor category, tertiary grade 5 in men with Gleason score 7 prostate cancer, and percent positive biopsies. Also, with 40 deaths in the overall study cohort of which 9 could not be attributed to prostate cancer, a competing risk[5] and not Cox regression analysis[4] would have been more appropriate to analyze the end point of time to first failure or prostate cancer death. Finally, treatment use varied, in that some men could have received irreversible and life-long testosterone suppression via bilateral orchiectomy as compared with 2 years of reversible ADT using a luteinizing hormone-releasing hormone agonist. Moreover, in men in whom EBRT was delivered, the prostate was always treated whereas the pelvic LNs were

En attente études en cours

RT + HT
= standard

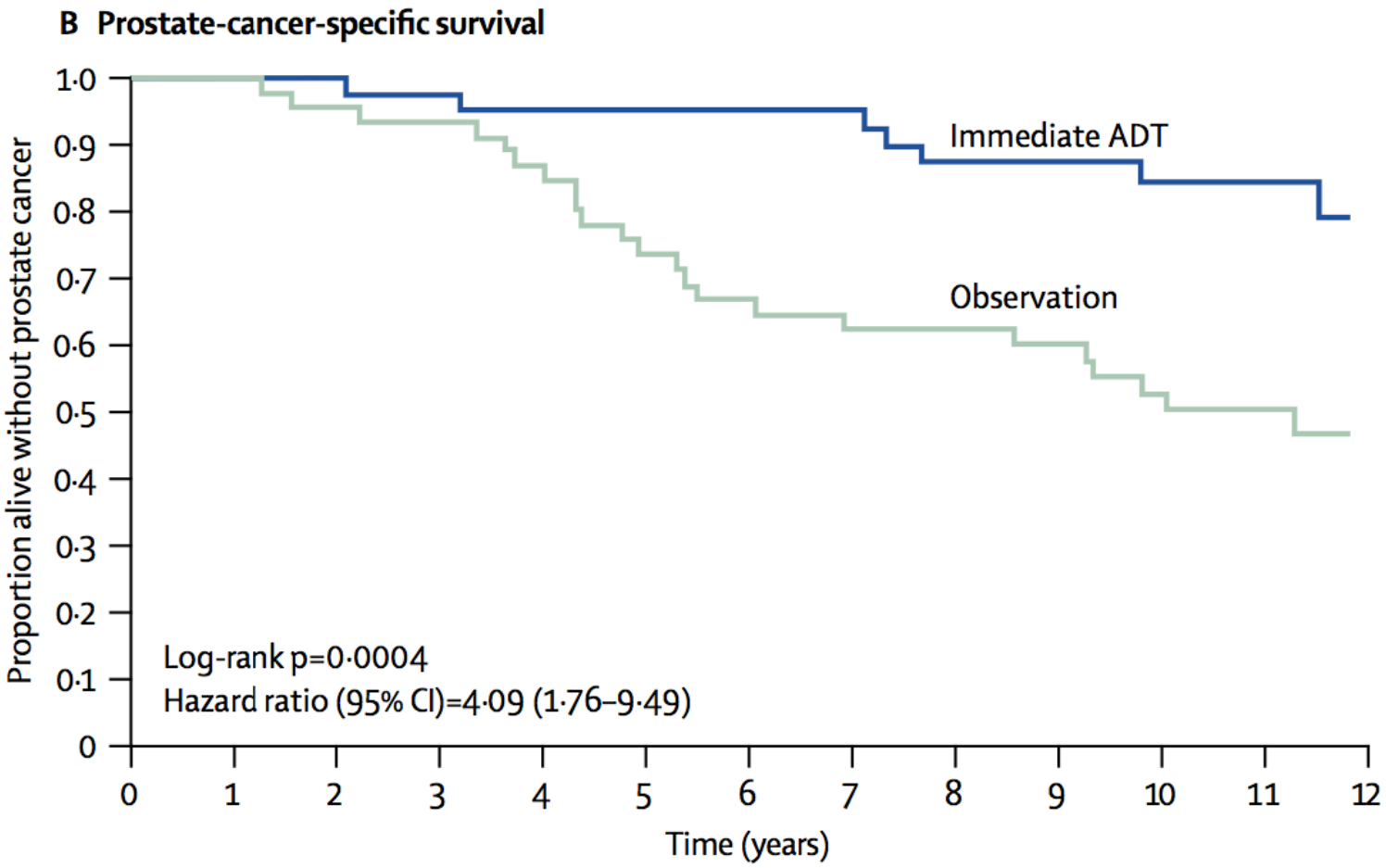
?

HT
= standard

Place RT ?
GETUG 21
Stampede

pN1 : place de la radiothérapie ?

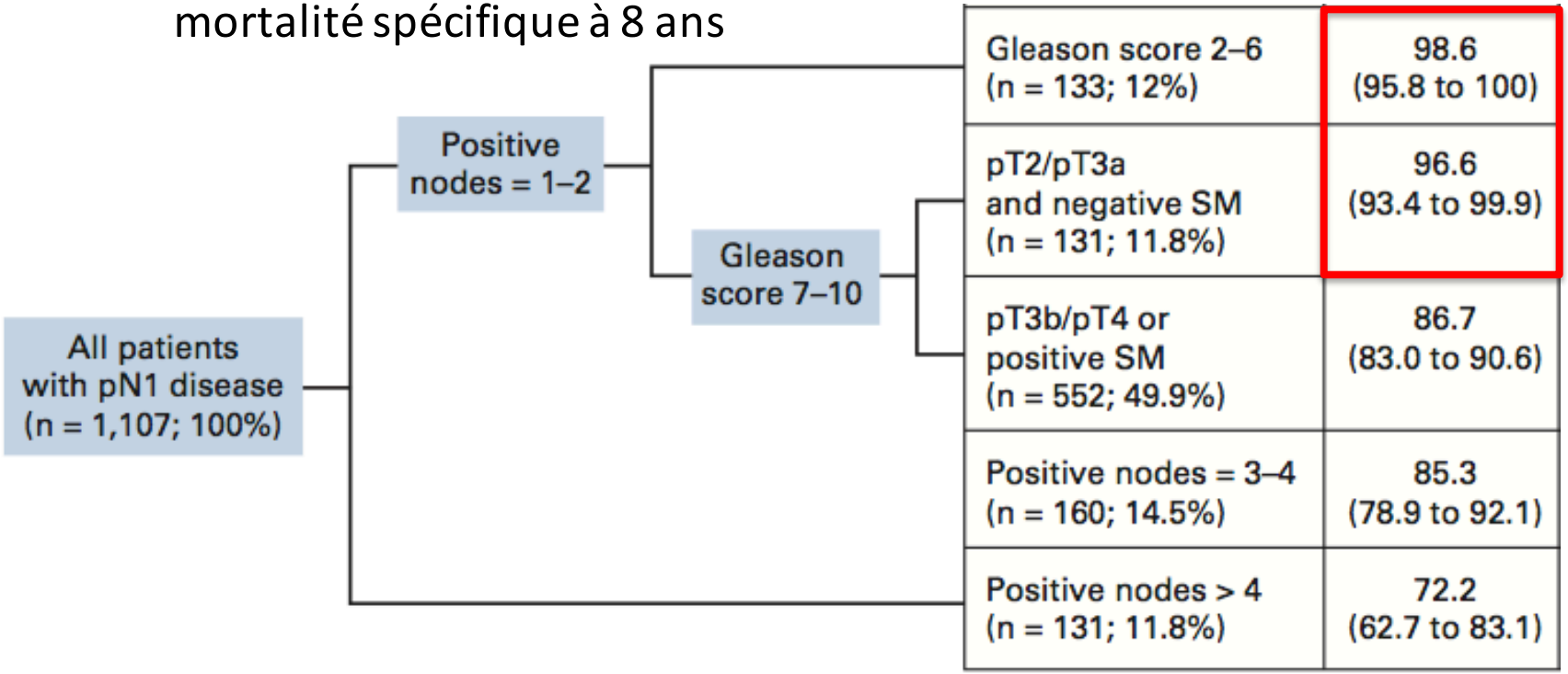
pN1
Hormonothérapie adjuvante = standard



Messing et al. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. Lancet Oncol (2006) vol. 7 (6) pp. 472-9

Peut-on guérir d'un cancer de prostate métastatique ganglionnaire simplement opéré?

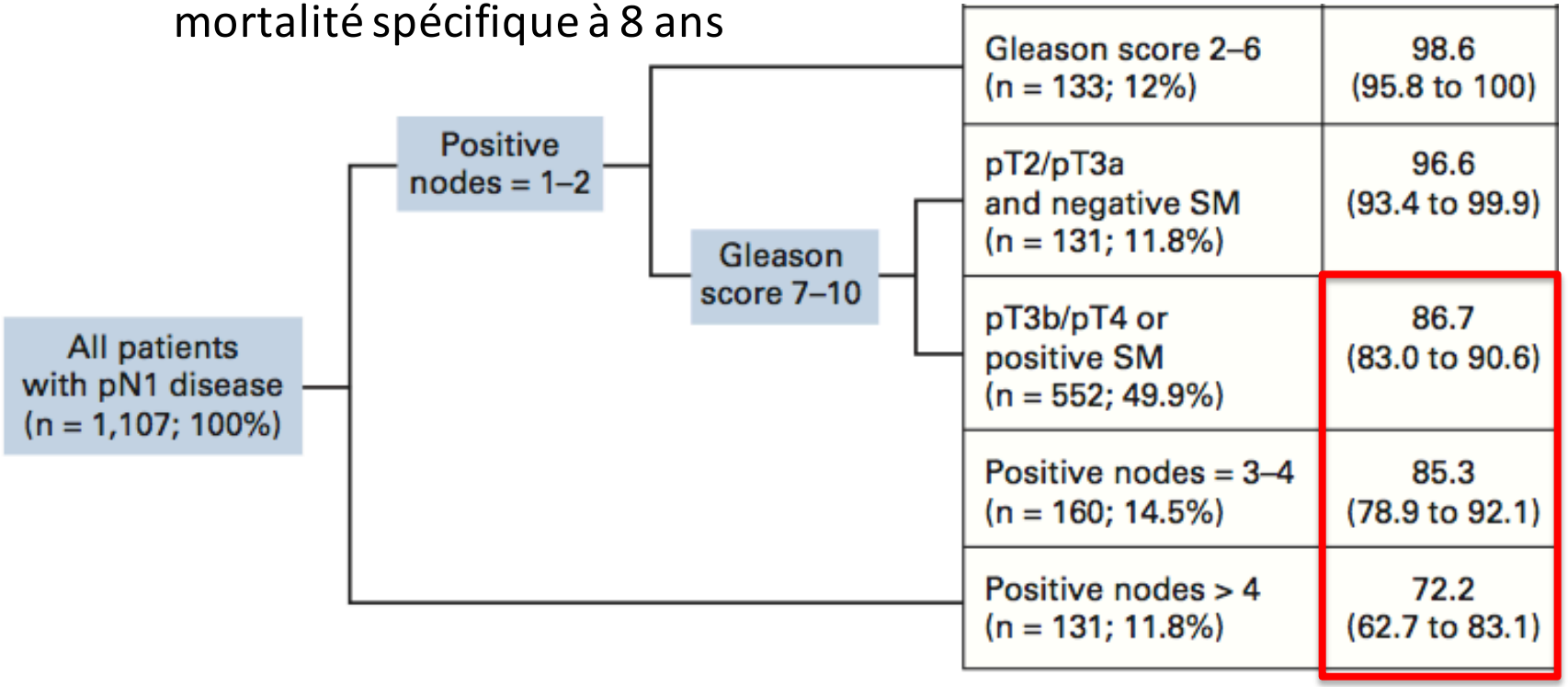
Chirurgie pN1
mortalité spécifique à 8 ans



Abdollah et al. Impact of Adjuvant Radiotherapy on Survival of Patients With Node-Positive Prostate Cancer. J Clin Oncol (2014)

Quelle est l'efficacité de Chirurgie+ Hormonothérapie?

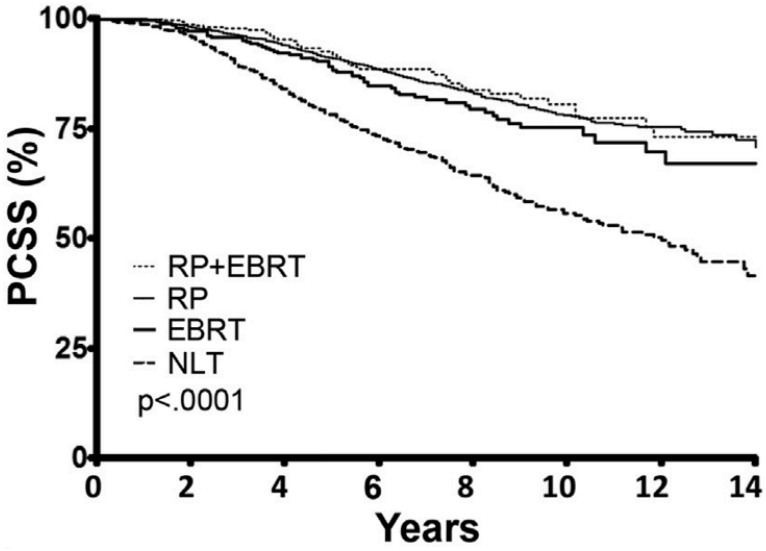
Chirurgie pN1
mortalité spécifique à 8 ans



Abdollah et al. Impact of Adjuvant Radiotherapy on Survival of Patients With Node-Positive Prostate Cancer. J Clin Oncol (2014)

Faut-il ajouter RT ?
Études en défaveur

SEER 1995 to 2007
577 hommes dont 177 avec RT adjuvante

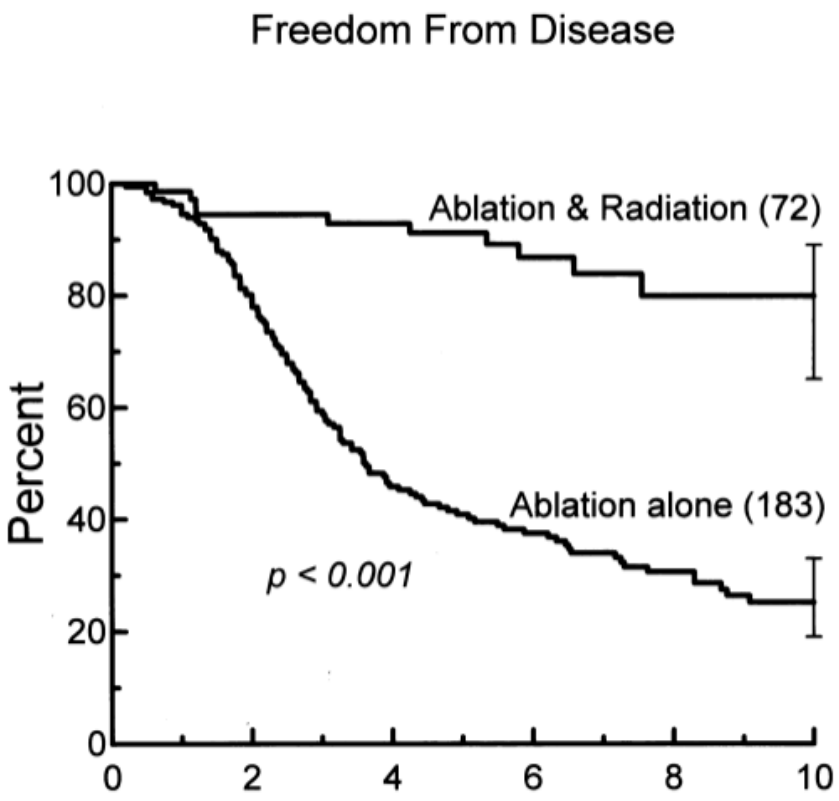


	After propensity weighting		
	No RT (*N* = 400)	ART (*N* = 177)	*P*
Overall mortality:			
Deaths	95	49	
Person-years follow-up	2520	964	
Deaths per 100 person-years	3.77	5.09	0.153
PCSM:			
Deaths	25	21	
Person-years follow-up	1908	726	
Deaths per 100 person-years	1.31	2.89	0.090
	No RT	**ART ≤12 months**	***P***
Overall mortality per 100 person-years	3.77	4.01	0.891
PCSM per 100 person-years	1.31	1.42	0.913
	No RT	**ART ≤24 months**	***P***
Overall mortality per 100 person-years	3.77	5.35	0.193
PCSM per 100 person-years	1.30	2.39	0.354

RT : Pas de bénéfice si pN1

- Rusthoven et al. The impact of definitive local therapy for lymph node-positive prostate cancer: a population-based study. IJROBP (2014) vol. 88 (5) pp. 1064-73
- Kaplan et al. Patterns of care and outcomes of radiotherapy for lymph node positivity after radical prostatectomy. BJU International (2013) vol. 111 (8) pp. 1208-14

Données rétrospectives en faveur RT



255 pts

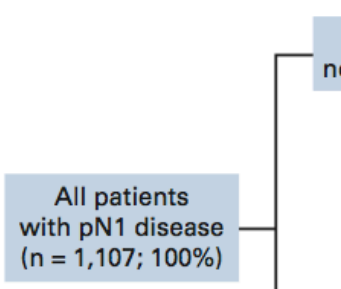
Curage gg stoppé si extempo pN1

HT+RT vs HT seule

- survie globale 10 ans (67 % vs 46%, p =0,008)
- contrôle local (89 % vs49%, p<0,001)
- survie sans méta (85% vs 56%, p= 0,006)

Zagars et al. Addition of radiation therapy to androgen ablation improves outcome for subclinically node-positive prostate cancer. Urology (2001) vol. 58 (2) pp. 233-9

Patients pN1 : Bénéfice RT+HT adjuvante dans population sélectionnée ?



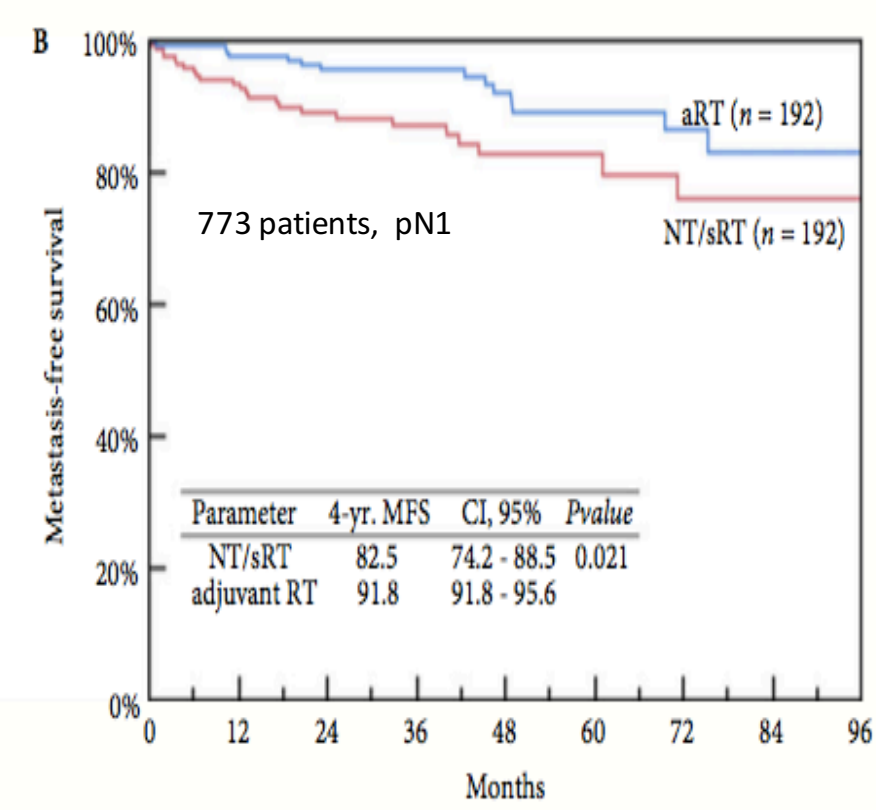
Eight-Year CSM-Free Survival (95% CI)

	Entire Cohort	aHT Alone	aRT + aHT	*P*
Gleason score 2–6 (n = 133; 12%)	98.6 (95.8 to 100)	98.4 (95.4 to 100)	100 (100 to 100)	.7
pT2/pT3a and negative SM (n = 131; 11.8%)	96.6 (93.4 to 99.9)	96.8 (93.2 to 100)	96.3 (89.4 to 100)	.4
pT3b/pT4 or positive SM (n = 552; 49.9%)	86.7 (83.0 to 90.6)	84.2 (79.7 to 89.0)	93.1 (87.5 to 99.1)	.03
Positive nodes = 3–4 (n = 160; 14.5%)	85.3 (78.9 to 92.1)	78.8 (69.7 to 89.0)	96.5 (91.8 to 100)	.02
Positive nodes > 4 (n = 131; 11.8%)	72.2 (62.7 to 83.1)	72.0 (60.9 to 85.2)	74.7 (59.2 to 94.3)	.9

- Da Pozzo, et al. Long-term follow-up of patients with prostate cancer and nodal metastases treated by pelvic lymphadenectomy and radical prostatectomy: the positive impact of adjuvant radiotherapy. *Eur Urol* 2009; 55: 1003–11
- Briganti et al., Combination of adjuvant hormonal and radiation therapy significantly prolongs survival of patients with pT2-4 pN+ prostate cancer: results of a matched analysis. *Eur Urol* 2011; 59: 832–40
- Abdollah et al. Impact of Adjuvant Radiotherapy on Survival of Patients With Node-Positive Prostate Cancer. J Clin Oncol (2014)

RT adjuvante ou rattrapage ?

RT adjuvante vs RT rattrapage: Bénéfice en survie sans métastase

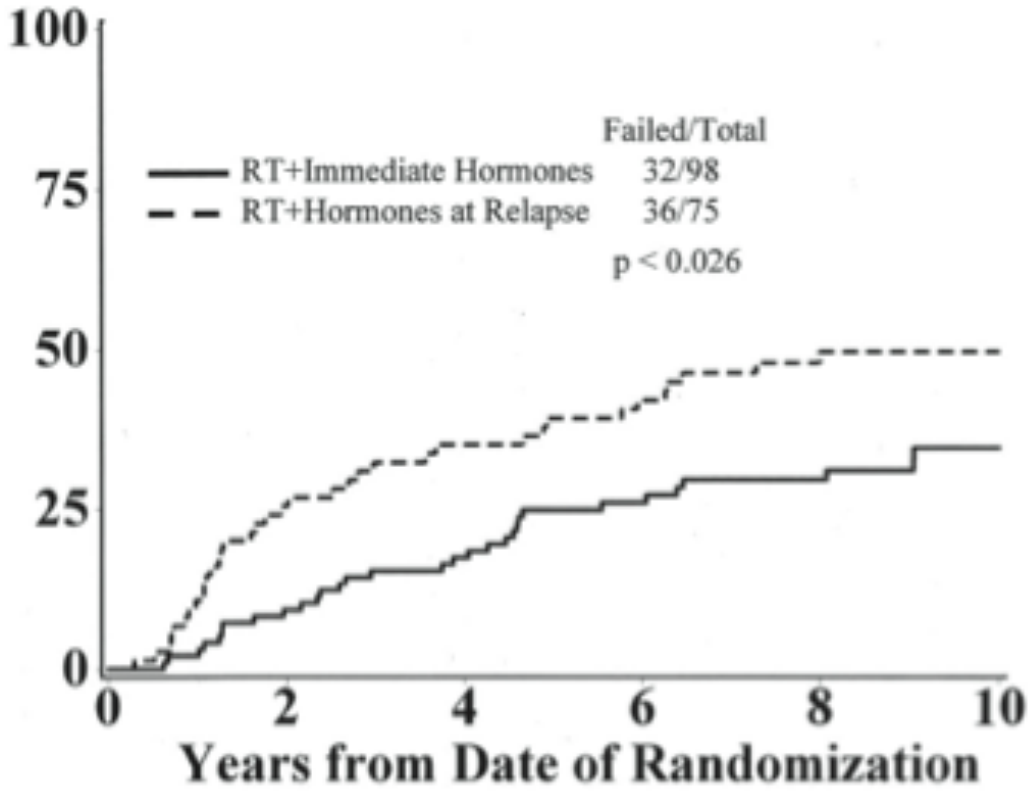


Sans influence du nb de ganglions

Characteristic	Metastasis-free survival		
	HR	95% CI	P
Year of surgery	0.98	0.87–1.11	0.753
Preoperative PSA			
10–20 vs <10 ng/mL	0.66	0.33–1.31	0.236
>20 vs <10 ng/mL	1.06	0.54–2.06	0.869
pT-stage			
≥pT3b vs pT2/pT3a	1.11	0.53–2.34	0.783
Surgical margin			
Positive vs negative	1.12	0.57–2.17	0.744
Gleason score			
≥8 vs ≤7	1.82	1–3.32	0.051
Positive LNs			
2 vs 1	1.06	0.51–2.24	0.872
3 vs 1	1.08	0.4–2.93	0.879
4 vs 1	0.37	0.05–2.87	0.341
≥5 vs 1	1.73	0.8–3.75	0.163
Treatments			
NT/early sRT vs aRT	2.70	1.23–5.88	0.013
aHT vs NT/early sRT	1.18	0.52–2.56	0.69
aHT vs aRT	3.18	1.45–6.95	0.004
Additional HT			
Yes vs no	7.26	3.25–16.21	<0.001

Tilki, D. *et al.* Adjuvant radiation therapy is associated with better oncological outcome compared with salvage radiation therapy in patients with pN1 prostate cancer treated with radical prostatectomy. *BJU Int* **119,** 717–723 (2017).

Faut-il systématiquement combiner RT + HT ?



Patients pN1 post curage

Lawton et al. Androgen suppression plus radiation versus radiation alone for patients with stage D1/pathologic node-positive adenocarcinoma of the prostate: updated results based on national prospective randomized trial Radiation Therapy Oncology Group 85-31. Journal of clinical oncology (2005) vol. 23 (4) pp. 800-7

cN1 et pN1 : Questions en suspens ?

- Peut-on se passer de preuve histologique/curage ganglionnaire si RT envisagée?
- Prostate seule ?
- Prostate et aires ganglionnaires pelviennes ?
- RT externe ? Curiethérapie ?
- Quelles limites pour les aires ganglionnaires ?
- Quelle dose totale ?
- Augmentation de la dose sur les adénopathies suspectes ?
- Quelle séquence d'administration ? Quelle durée d'hormonothérapie ?

Conclusion

Recommandations :
HT = standard; RT = option raisonnable

European Association of Urology

N1 patients		
cN1	In patients with cN+ PCa, offer pelvic EBRT in combination with immediate long-term ADT.	B
pN1 after eLND	Offer adjuvant ADT for node-positive (pN+).	A
	Offer adjuvant ADT with additional radiotherapy.	B
	Offer observation (expectant management) to a patient after eLND and ≤ 2 nodes showing microscopic involvement, with a PSA < 0.1 ng/mL and absence of extranodal extension.	B

NCCN National Comprehensive Cancer Network®

Regional:
Any T, N1, M0 → **EBRT^{h} + ADT^{I} (2–3 y) (category 1)** or **ADT^{I}**

Merci de votre attention !

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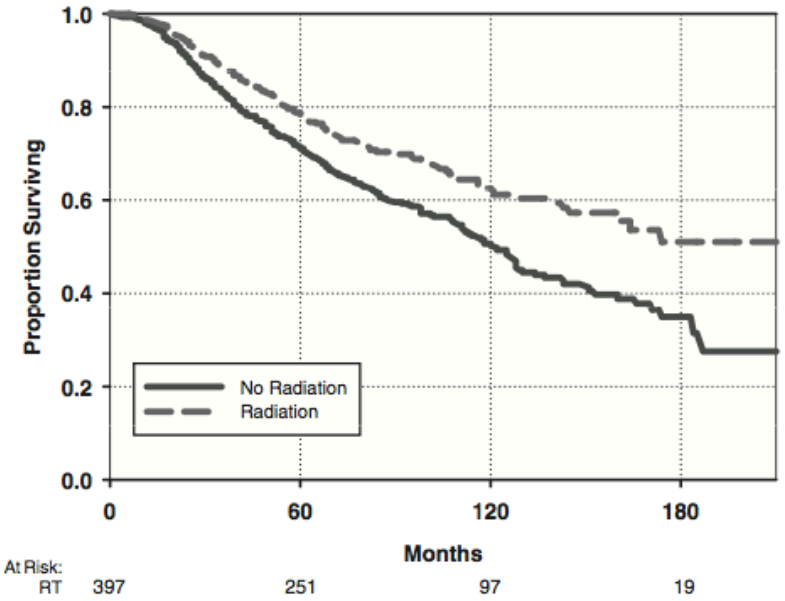
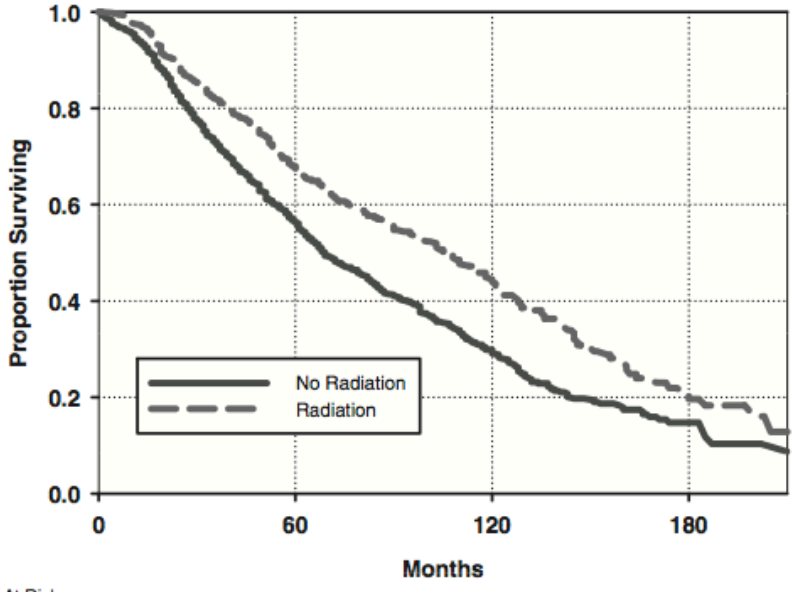
Survie spécifique



Survie globale



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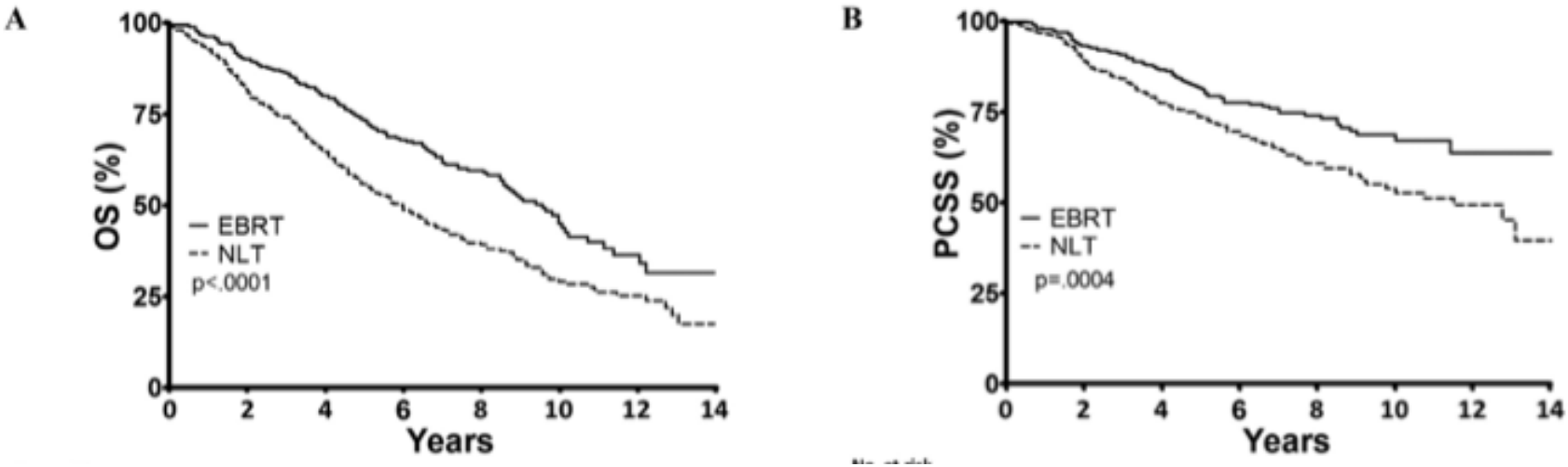

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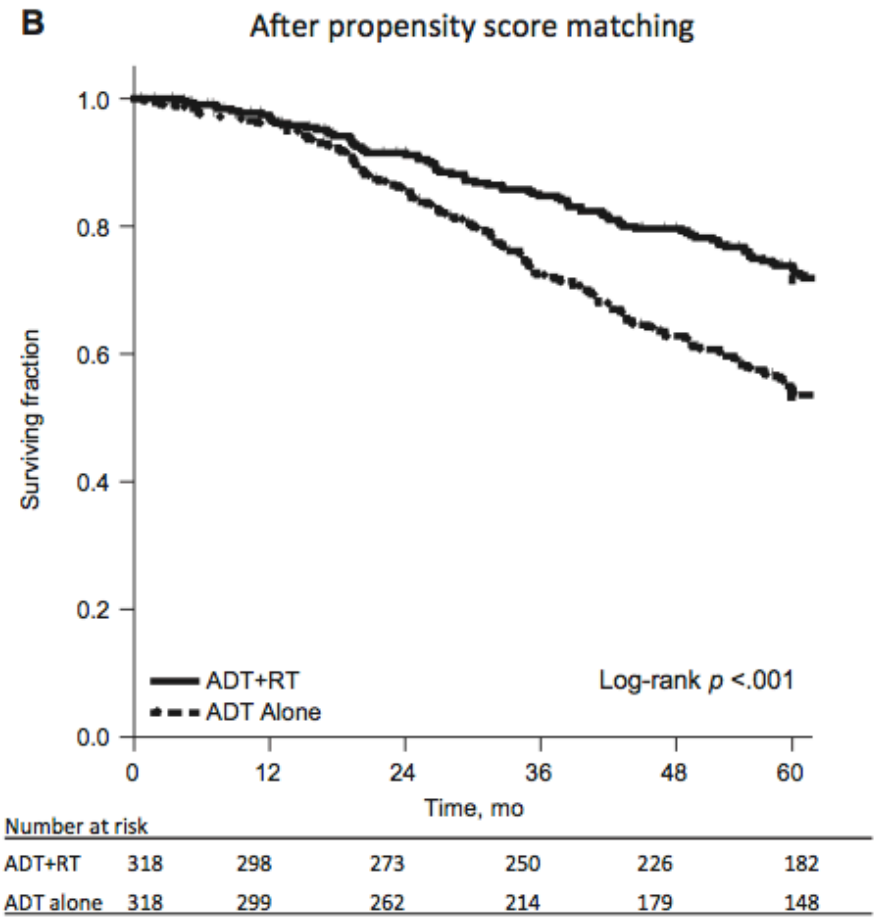

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RT = +20 % à 5 ans

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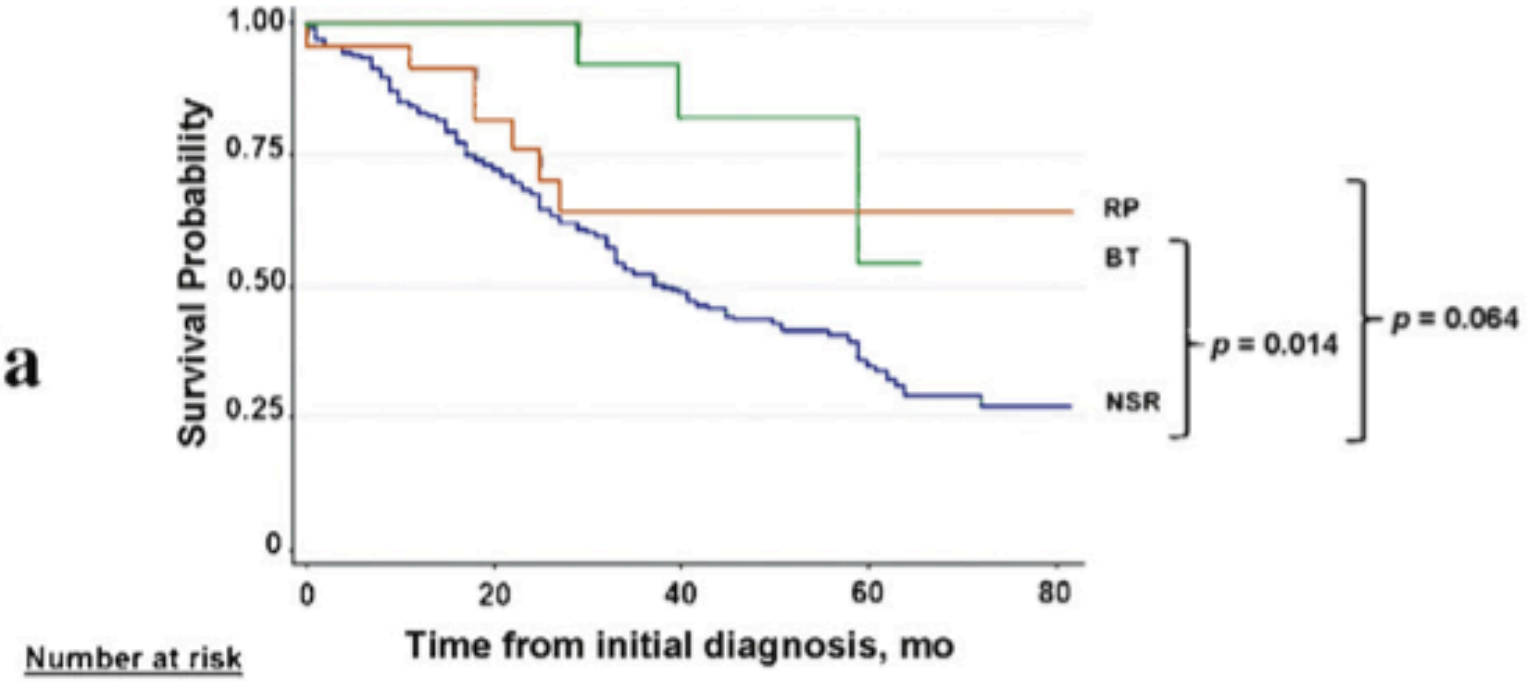
Métastases ganglionnaires extra pelviennes (M1a): faut-il un traitement local ?

M1a



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)