

Prise en charge du cancer de la prostate a haut risque

Alger le 09 Juin 2022

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Chef de service de radiotherapie

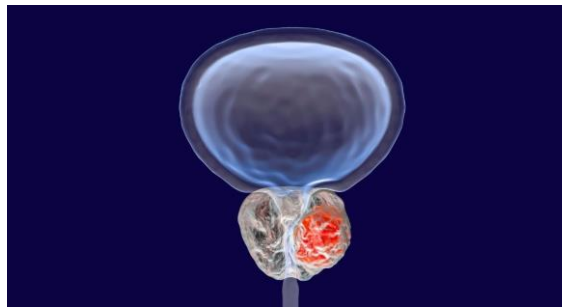
CLCC Annaba



Introduction :

- Le cancer de la prostate représente la deuxième cause de décès par cancer chez l'homme dans la plupart des pays développés.
- Son incidence est en augmentation constante ,En Algérie, les registres du cancer le placent au 4ème rang.
- La radiothérapie occupe une place centrale dans la prise en charge des formes localement avancées et à haut risque des cancers de la prostate
- L'association Radiothérapie- Hormonothérapie longue est un standard dans la prise en charge de ces cancers

Les formes localement avancées et à haut risque



La classification de d'Amico: la base de la stratégie thérapeutique

T1-T2
Gleason 6
PSA \leq 10 ng/ml

Favorable



- Surveillance active
- Prostatectomie
- Curiethérapie
- Radiothérapie

T1-T2
Gleason 7
Ou PSA 10-20 ng/ml

Intermédiaire



- Prostatectomie
- Radiothérapie \pm HT
- Courte
- (Surveillance active?)

T3-T4
Ou Gleason 8-10
Ou PSA $>$ 20 ng/ml

Défavorable



- Radiothérapie et
Hormono. Longue
- Prostatectomie

Message N°1: C'est quoi une forme à haut risque ?

| | Very low-risk | Low-risk | Intermediate-risk | High-risk |
|-----------------|--|---|---|---------------------------------------|
| D'Amico (2) | | PSA \leq 10 ng/mL and GS < 7 and cT1-2a | PSA 10-20 ng/mL or GS \leq 7, or cT2b | PSA > 20 ng/mL, or GS > 7, or cT2c-3a |
| NCCN (3) | cT1c, GS < 7, PSA < 10 ng/mL, PSAD < 0.15, < 3 positive biopsies | PSA < 10 ng/mL, GS < 7, cT1-2a | PSA 10-20 ng/mL, or GS 7, or cT2b-2c | PSA > 20 ng/mL, or GS > 7, or cT3a |
| CAPRA score (4) | | < 3 | 3-5 | 6-10 |
| EAU (5) | | PSA < 10 ng/mL, GS < 7, cT1c | PSA 10-20 ng/mL, or GS 7, or cT2b-2c | PSA > 20 ng/mL, GS 8-10 or = > cT3a |

Autres facteurs pronostique

- Autres facteurs

- % de grade 4
- % de grade 5
- Nbre de biopsies positives

- Facteurs associés

- Comorbidités
- Fonction urinaire
- Fonction sexuelle
- Entourage social
- Projet de vie ...

Une adaptation nécessaire ...

Groupe défavorable :

Table 4. Rate of prostate cancer death as a function of the different definitions of high-risk disease

| Risk factor | Yes/No | n | Prostate cancer death | | | |
|-----------------------------------|--------|-----|-----------------------|-------------|--------------|----------------|
| | | | 5-year | 8-year | p value* | HR (95% CI) |
| Overall | — | 718 | 3% (2–4) | 8% (6–10) | — | — |
| Gleason score 8–10 | Yes | 145 | 13% (10–16) | 21% (16–26) | $p < 0.0001$ | 7.0 (2.9–16.8) |
| | No | 573 | 0.5% (0.2–0.9) | 5% (3–7) | | |
| Gleason Pattern 5 | Yes | 76 | 25% (19–31) | 45% (36–54) | $p < 0.0001$ | 16.2 (4.3–61) |
| | No | 639 | 1% (0.5–1.5) | 4% (3–5) | | |
| PSA >20 ng/mL | Yes | 121 | 6% (3–9) | 19% (14–24) | $p < 0.0001$ | 3.8 (1.7–8.4) |
| | No | 595 | 2% (1–3) | 4% (3–5) | | |
| cT3/4 | Yes | 81 | 10% (6–14) | 24% (18–30) | $p < 0.0001$ | 3.7 (1.6–8.5) |
| | No | 636 | 2% (1–3) | 5% (4–6) | | |
| NCCN high risk | Yes | 234 | 8% (6–10) | 18% (14–22) | $p < 0.0001$ | 6.9 (3.5–13.4) |
| | No | 483 | 0.4% (0.1–0.8) | 2% (1–3) | | |
| Number of NCCN high-risk features | 1 | 145 | 5% (3–7) | 12% (8–16) | $p < 0.002$ | 4.8 (1.8–12.6) |
| | 2 | 64 | 8% (4–12) | 20% (14–26) | | |
| Number of NCCN high-risk features | 1 | 145 | 5% (3–7) | 12% (8–16) | | |
| | 2 | 64 | 8% (4–12) | 20% (14–26) | | |
| | 3 | 25 | 19% (10–28) | 39% (27–51) | | |

Abbreviations: HR = hazard ratio; CI = confidence interval; PSA = prostate-specific antigen; NCCN = National Comprehensive Cancer Network.; PFP = Progression Free Probability at 5-years

* Log-rank test.

Groupe défavorable

Table 1 – Definitions of *high-risk prostate cancer*

| Source | Definition |
|---|--|
| D'Amico et al. [8] | PSA \geq 20 ng/ml or GS 8–10 or clinical stage \geq T2c |
| American Urological Association [2] | PSA \geq 20 ng/ml or GS 8–10 or clinical stage \geq T2c |
| National Comprehensive Cancer Network [18] | PSA \geq 20 ng/ml or GS 8–10 or clinical stage \geq T3 or any two of the following: T2b/c, GS 7, PSA 10–20 ng/ml |
| European Association of Urology [1] | PSA \geq 20ng/ml or biopsy GS 8–10 or clinical stage \geq T3a |
| Radiation Therapy Oncology Group [19] | PSA 20–100 ng/ml, biopsy GS 8–10, and any clinical stage or clinical stage \geq T2c or PSA < 100 ng/ml and GS 8–10 |
| Cancer of the Prostate Risk Assessment Score [23] | Age, PSA, clinical stage, biopsy GS, percentage of positive biopsy cores |

PSA = prostate-specific antigen; GS = Gleason score.

Individualiser:

- Les cT3-T4: « localement avancés » - peu chirurgicaux
- Les cT1-T2 « haut risques » - bons candidats pour la chirurgie?

La classification d'Amico toujours utile ,mais dépassée Sub-diviser les groupes

Data base canadienne (n=7,974)

Favorable

Très favorable
PSA \leq 6

Favorable
PSA: 6-10

Intermédiaire

Faible

1/ PSA \leq 10
2/ PSA>10 mais
Gleason6
et T1-T2a/b

Fort

PSA>10 et:
1/ Gleason 7
Ou 2/ T2c

Défavorable

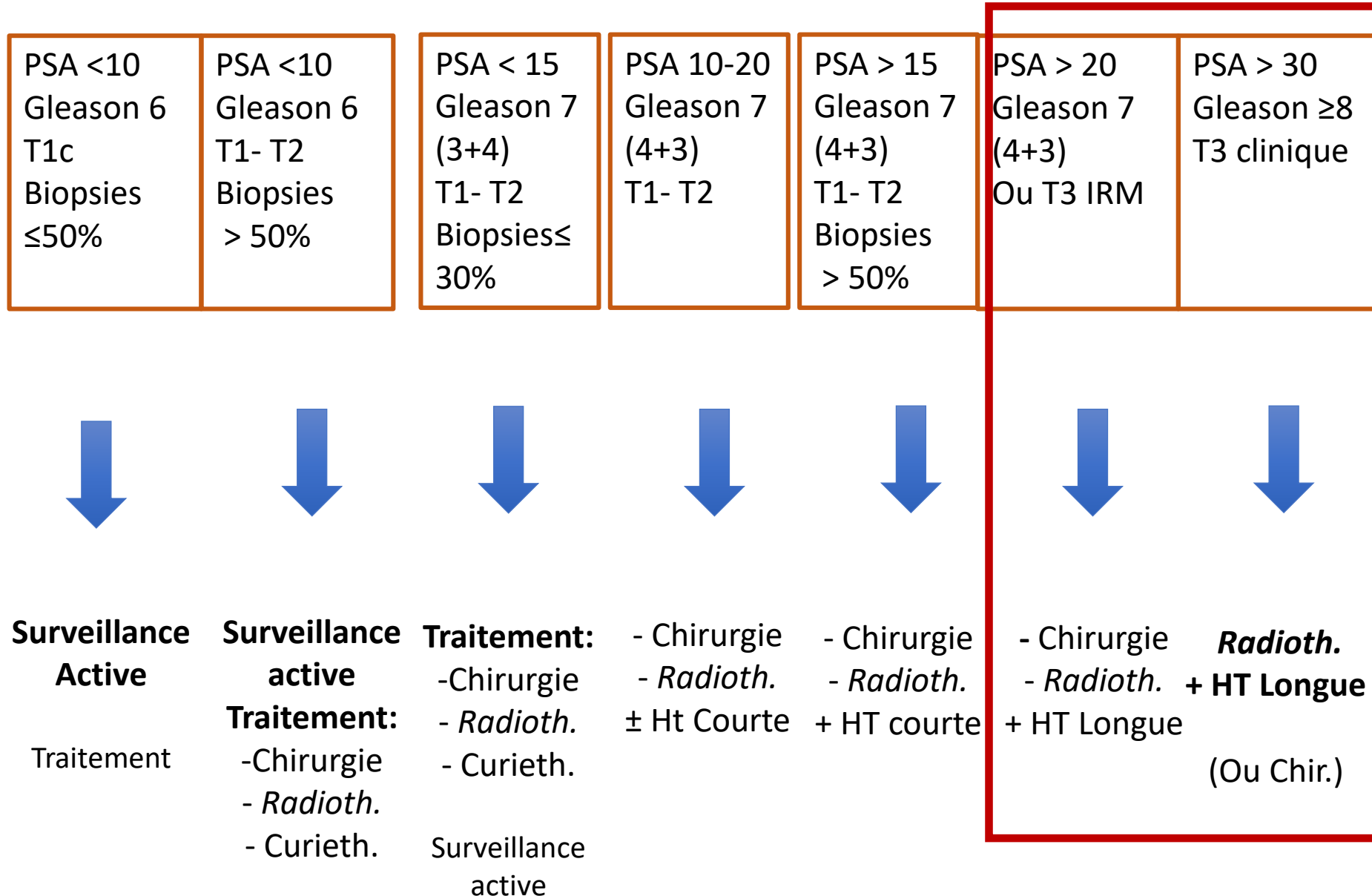
Faible

PSA20-30
Nbre biopsies <87.5%

Fort

PSA \geq 30
Biopsies \geq 87.5+

Groupes pronostiques et CAT



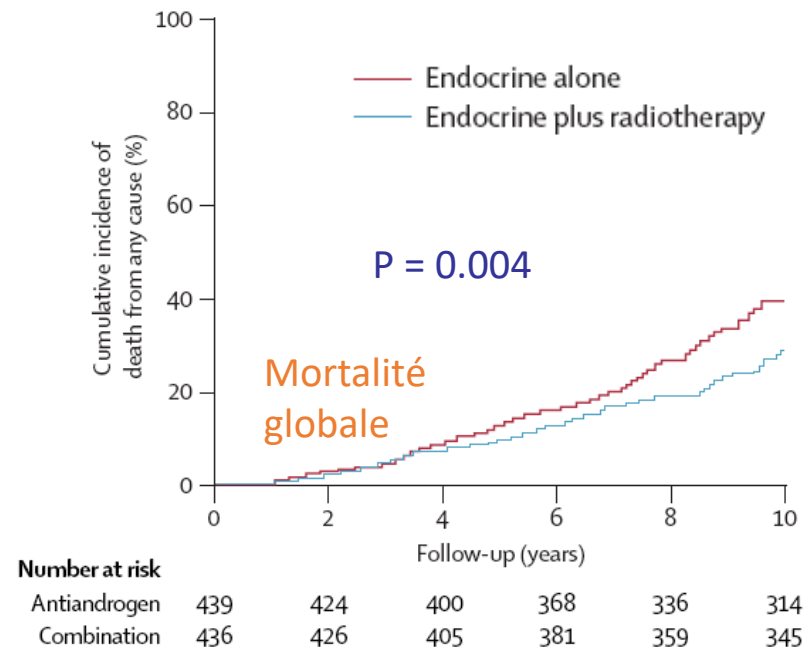
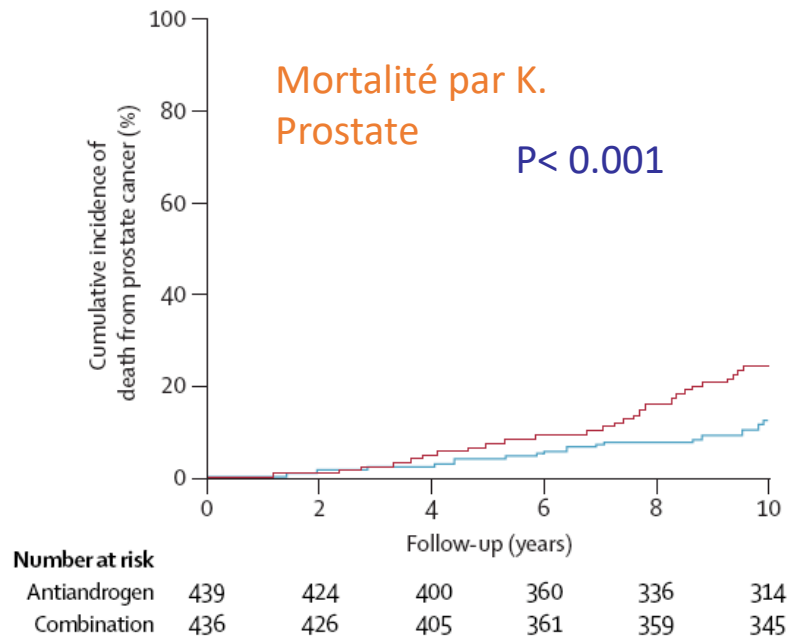
Message N°2

traitement local +++ par radiothérapie

- 3 essais randomisés
- HT vs HT+RT:
 - Widmark
 - Warde
 - Mottet
- Bénéfice en survie globale et/ou en
Survie sans récurrence dans les 3 essais

Cancers à haut risque: La RT est-elle nécessaire?

- Essai randomisé N° 1:
 - Widmark, Lancet, 2009, 373: 301-308
- 875 pts avec un K prostate localement avancé
- BAC 3 mois puis flutamide \pm RT



Cancers à haut risque: La RT est-elle nécessaire?

- Essai randomisé N° 2:
- 1205 pts avec un K prostate localement avancé
- Agonistes LH-RH 3 ans \pm RT

Warde, Lancet, 2011: 378: 2104-2111

Mason, JCO, 2015, 33: 2143-50

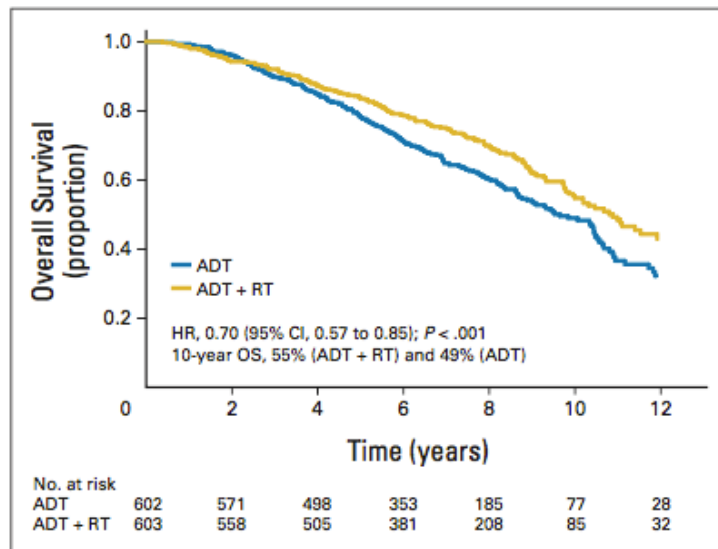


Fig 2. Overall survival (OS). ADT, androgen-deprivation therapy; HR, hazard ratio; RT, radiotherapy.

Overall survival

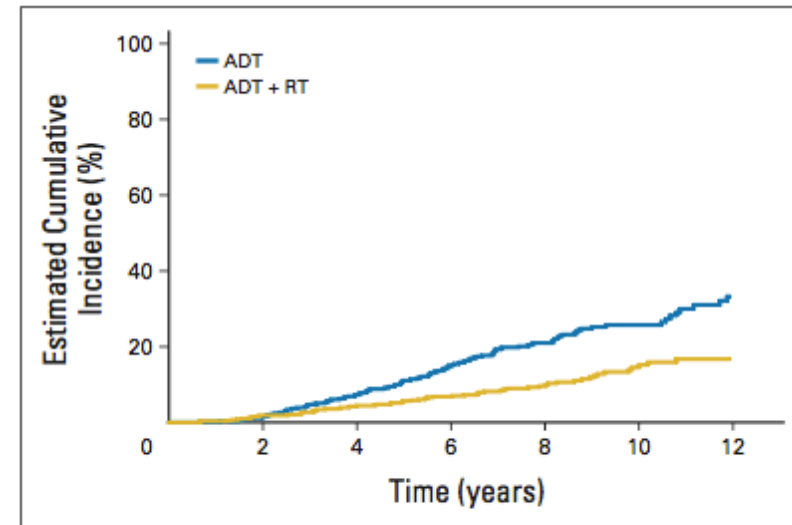
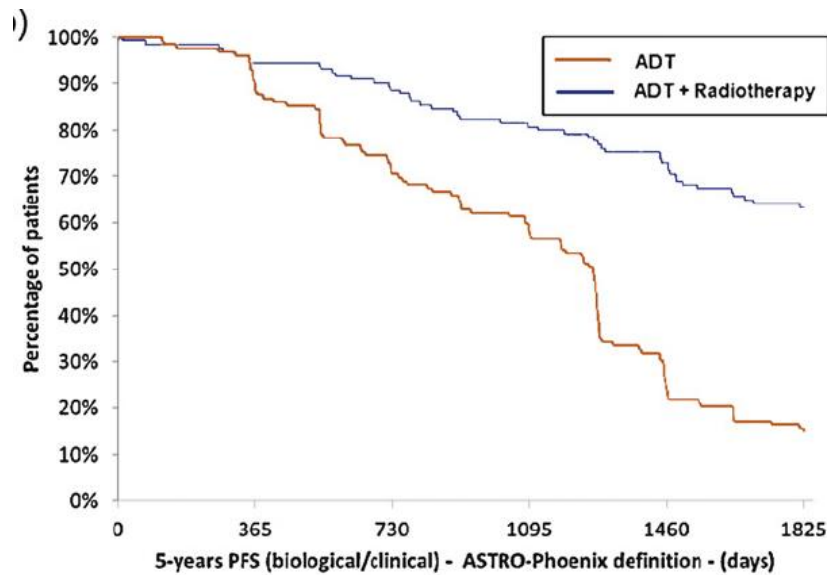


Fig 3. Deaths from prostate cancer. ADT, androgen-deprivation therapy; RT, radiotherapy.

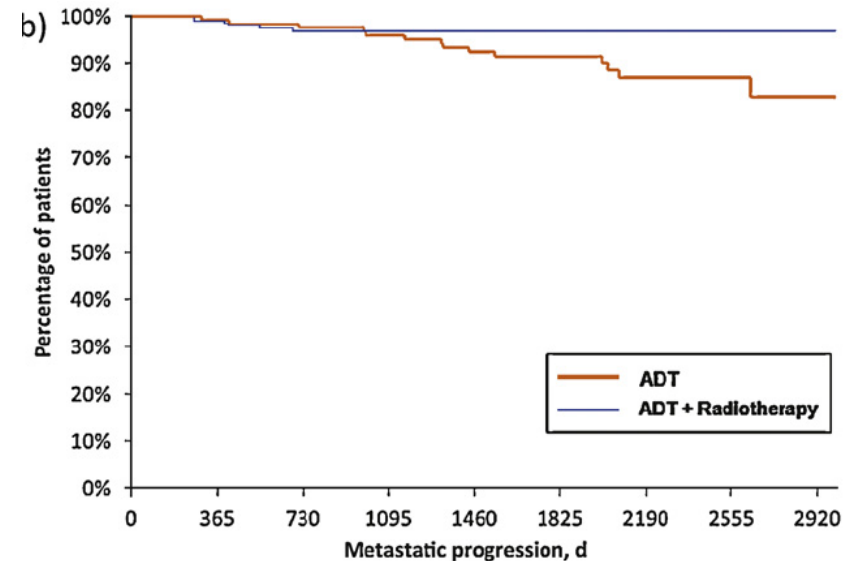
Disease-specific survival

Cancers à haut risque: La RT est-elle nécessaire?

- Essai randomisé N° 3:
- 266 pts avec un K prostate localement avancé
- Agonistes LH-RH 3 ans \pm RT

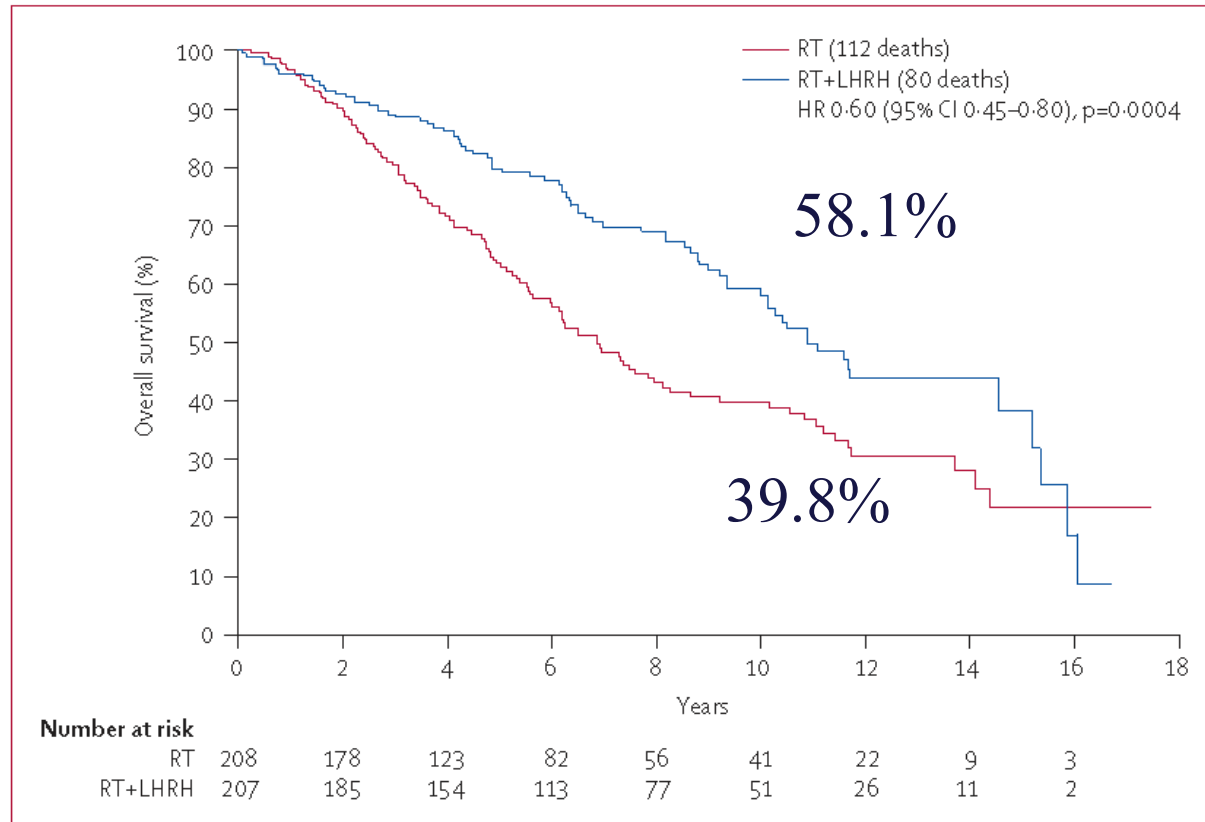


| Years | 0 | 1 | 2 | 3 | 4 | 5 |
|----------|-----|-----|-----|-----|----|----|
| ADT | 130 | 116 | 91 | 75 | 31 | 19 |
| ADT + RT | 133 | 124 | 115 | 102 | 92 | 67 |



| Years | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|----------|-----|-----|-----|-----|-----|----|----|----|----|
| ADT | 130 | 122 | 119 | 110 | 103 | 87 | 42 | 24 | 6 |
| ADT + RT | 130 | 126 | 116 | 106 | 101 | 81 | 50 | 26 | 11 |

Association Radiothérapie- Hormonothérapie: Un bénéfice en survie prouvé



Gain en survie:

18.3%

Mortalité spécifique
à 10 ans: **10.3%**

Figure 3: Overall survival

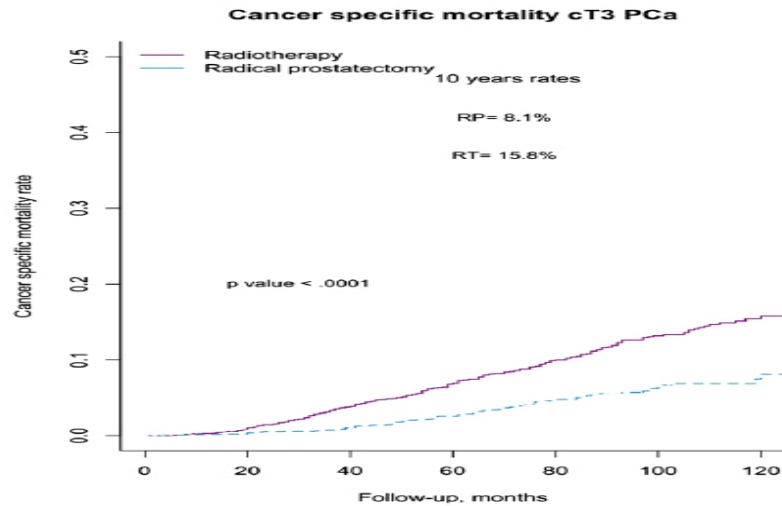
RT=radiotherapy. LHRH=luteinising-hormone-releasing hormone.

Etude EORTC: résultats à 10 ans

Traitement local: RT ou chirurgie ?

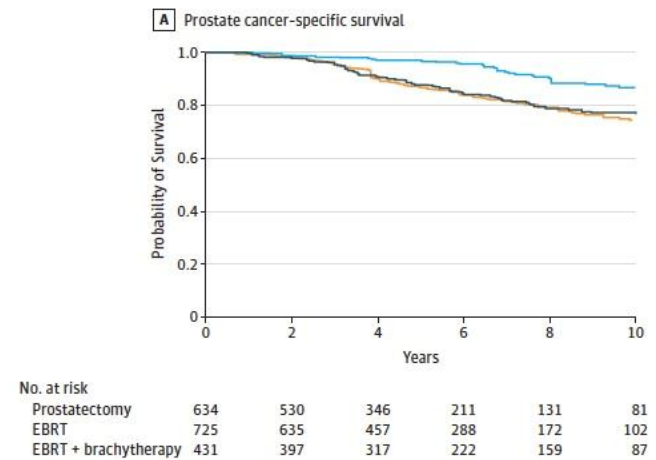
- Niveau de preuve: Radiothérapie
 - Plusieurs essais de phase III
 - Mais pas de comparaison directe
- Etudes rétrospectives

CHIR > RT+HT



SEER database
Bandini, World J Urol, 2018

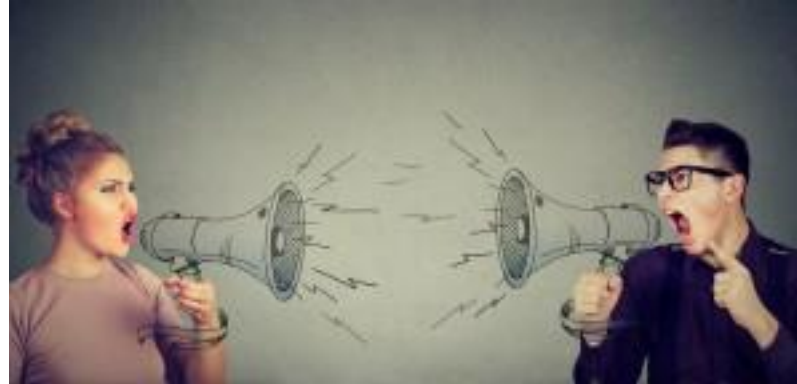
RT+brachyth. > RT ou CHIR
(Gleason 9-10)



Kishan, JAMA, 319: 896-905, 2018

Quel traitement local ?

- Faut-il polémiquer ?



- Quels sont les bonnes indications pour l'un ou l'autre des traitements



Discussion avec le patient

Déroulé de l'entretien avec le patient doit évoquer:

- Efficacité carcinologique
- Modalités du traitement
- Effets secondaires:
 - Urinaires
 - Sexuels
 - Digestifs
 - Autres



Qualité de vie

Seuls les patients peuvent répondre !!

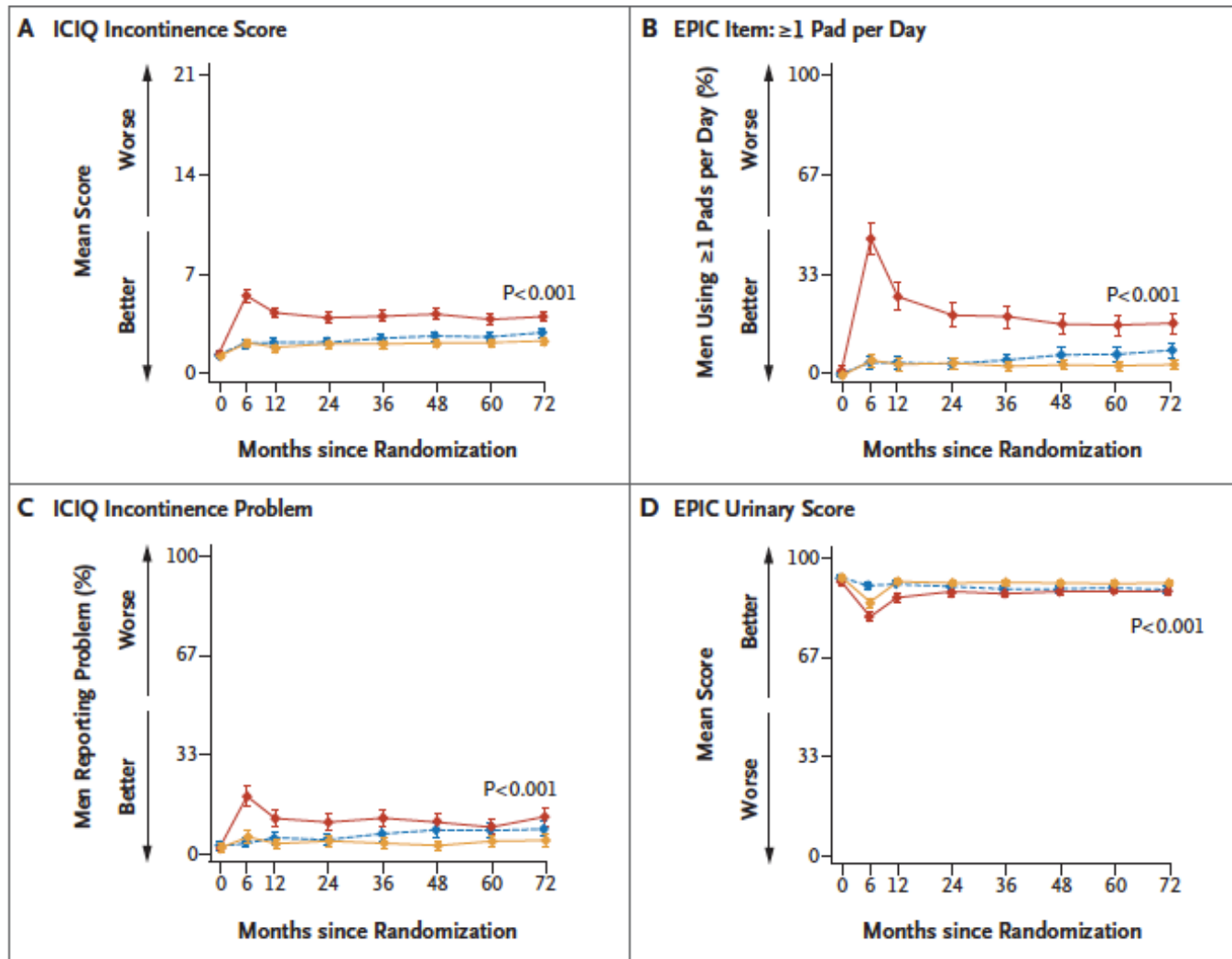
| Fréquence de l'effet secondaire | Médecins | Patients |
|---------------------------------|----------|----------|
| Incontinence (%) | 21 | 96 |
| Impuissance (%) | 52 | 96 |
| Fatigue | 10 | 75 |
| Diarrhée | 2 | 32 |

Patient-reported outcomes only !

Litwin, M. S., Lubeck, D. P., Henning, J. M. & Carroll, P. R. Differences in urologist and patient assessments of health related quality of life in men with prostate cancer: results of the CaPSURe database. *J. Urol.* 159, 1988–1992 (1998).

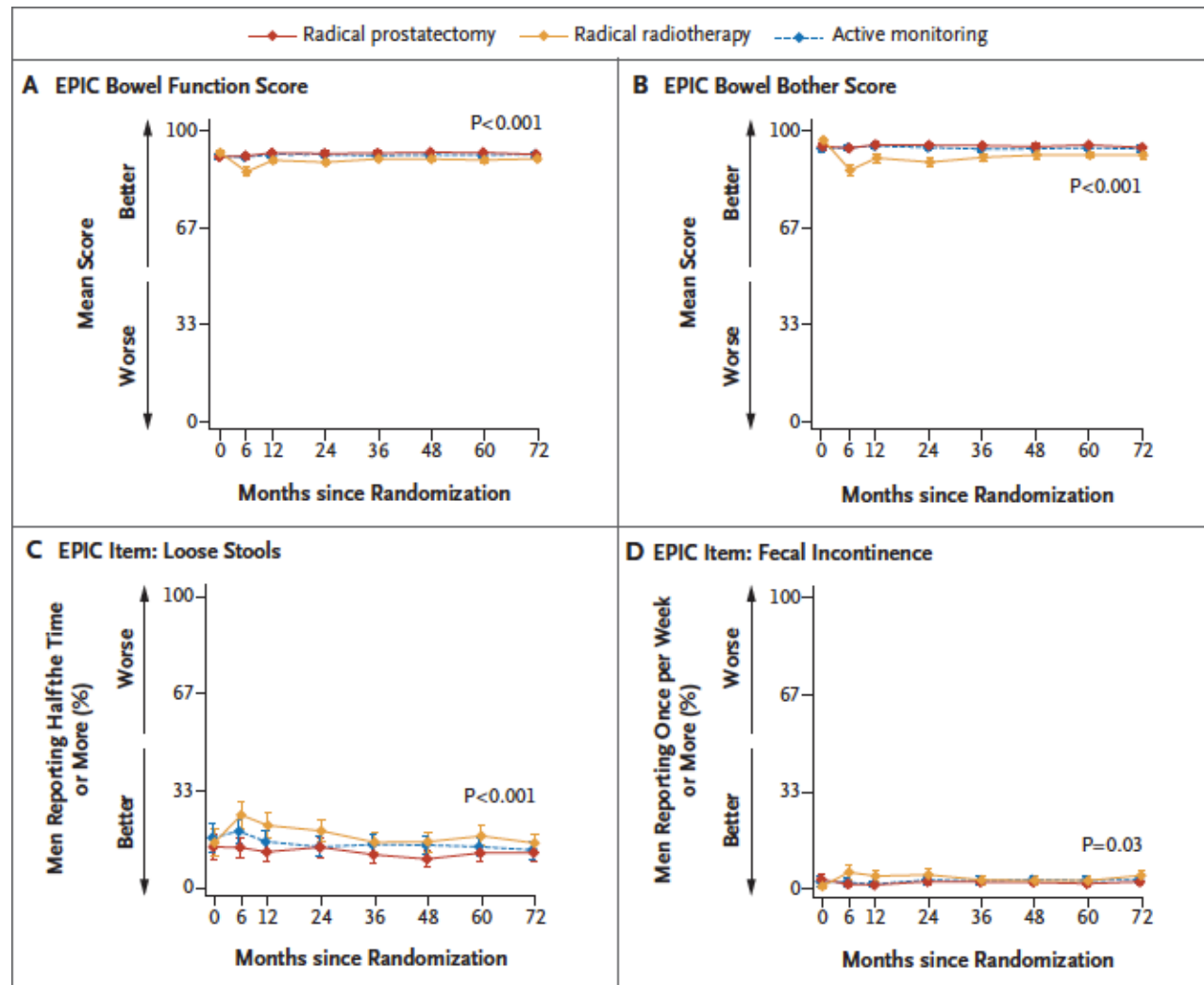
Qualité de vie & Complications

Qualité de vie: Incontinence



Donovan,
N Engl J Med.
2016 Oct
13;375(15):1425
-1437.

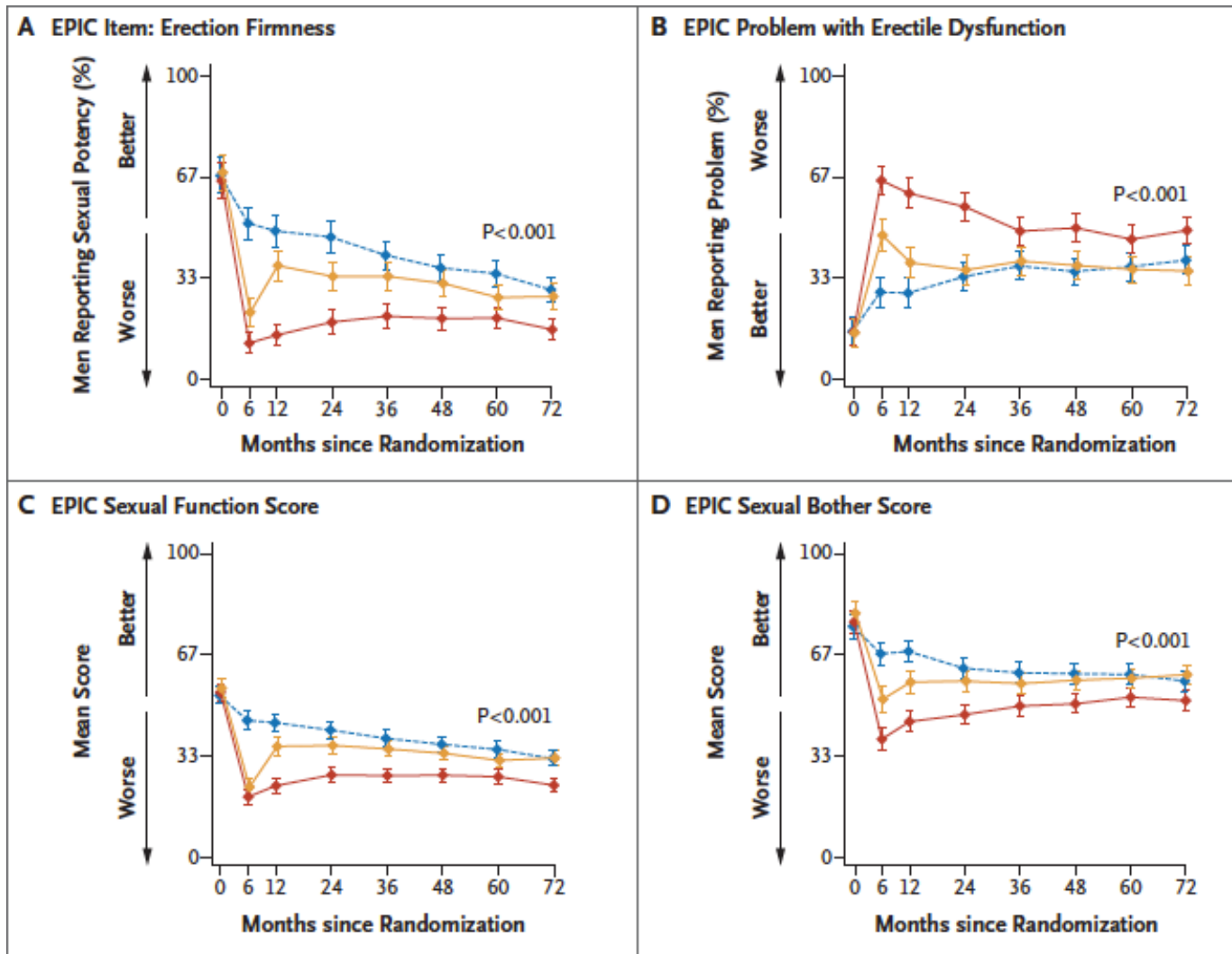
Qualité de vie : digestive



- Radical prostatectomy
- Radical radiotherapy
- Active monitoring

Donovan,
 N Engl J Med.
 2016 Oct
 13;375(15):1425
 -1437.

Qualité de vie: Sexualité



Donovan,
N Engl J Med.
2016 Oct
375(15):1425
-1437.

Cas clinique

- Patient de 62 ans
- Dosage systématique du PSA: 25 ng/ml (premier dosage)
- TR: Aspect de T3 à gauche
- Pas d'antécédent
- Sportif
- Trouble urinaire
- Scintigraphie osseuse et scanner TAP: normaux
- Biopsie de prostate: - Gleason 8 (4+4) – ISUP 4
- 9+/12 bilatérale
 - 6+/6 à gauche
 - 3+/6 à droite

IRM



Lésion prenant tout le lobe gauche de la base à l'apex.
NO MO

Que lui propose t'on?

➤ Chirurgie

ou

➤ Radiothérapie – Hormonothérapie

Stratégie multimodale chez les très hauts risques

Chirurgie



Radiothérapie

Aucune étude prospective randomisée à ce jour

| | | | |
|----------------------|------------------------------|---|---|
| High risk PCa | Watchful waiting | High risk localised: Watchful waiting may be offered to patients not eligible for local curative treatment and those with a short life expectancy. | |
| | | High risk locally advanced: In M0 patients unwilling or unable to receive any form of local treatment, a deferred treatment policy using ADT as monotherapy is feasible in asymptomatic patients with a PSADT > 12 mo and a PSA < 50 ng/mL and non-poorly differentiated tumour. | A |
| | Active surveillance | Not appropriate. | A |
| | Radical prostatectomy | NHT before RP is not recommended. | A |
| | | eLND should be performed in high-risk PCa. | A |
| | | Limited LND should not be performed. | A |
| | | High risk localised: In patients with high-risk localised PCa and a life expectancy of > 10 yrs, RP should be offered in a multimodality setting. | B |
| | | Nerve sparing surgery may be attempted in pre-operatively potent patients with low risk for extracapsular disease (refer to Partin tables/nomograms). | B |
| | | Multiparametric MRI may help in deciding when to perform nerve-sparing procedures in intermediate- and high-risk disease. | B |



High risk locally advanced: In highly selected patients with locally advanced PCa (cT3b-T4 N0 or any T N1), RP may be offered in a multimodality setting.

In patients with pT3,N0M0 PCa and an undetectable PSA following RP, adjuvant EBRT should be discussed as an option because it improves at least biochemical-free survival. *(The highest effect of adjuvant radiotherapy is seen in PCa patients with positive margins.)*

Patients with pT3,N0M0 PCa and an undetectable PSA following RP should be informed about salvage irradiation as an alternative to adjuvant EBRT irradiation when PSA increases.

Radiotherapy

In patients with **high-risk localised** PCa, the total dose is 76-78 Gy in combination with long-term ADT (2-3 yrs is recommended).

In patients with **locally advanced cN0** PCa, radiotherapy must be given in combination with long-term ADT (2-3 yrs is recommended).

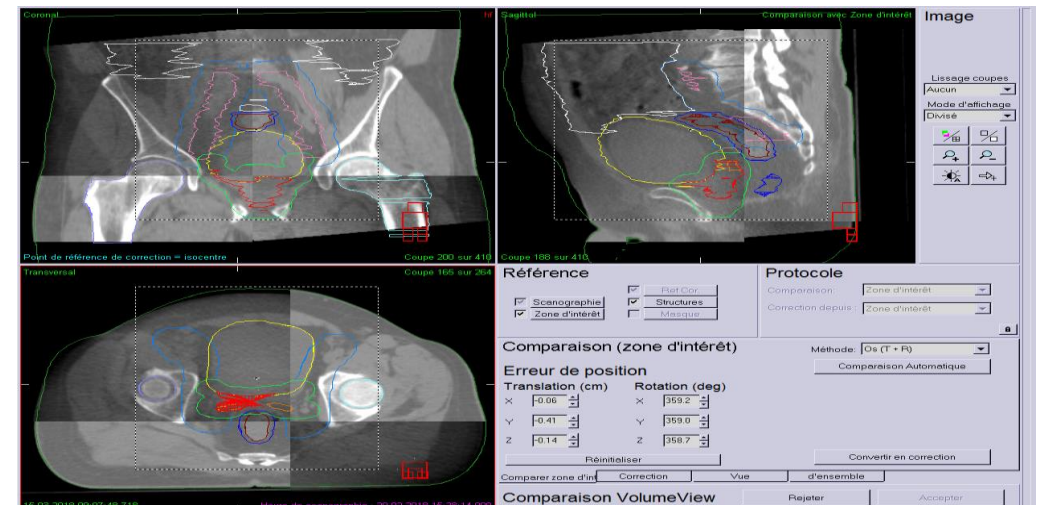
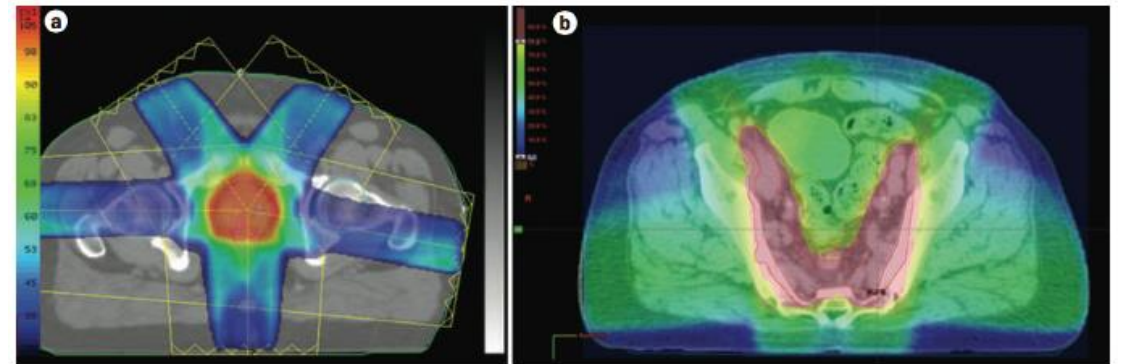
Arguments en faveur d'une radiotherapie

- Gleason:8(4+4)ISUP 4
 - Biopsie :9/12
 - T3
- ➡ defavorable fort ➡ RT+HT longue

Technique d'irradiation

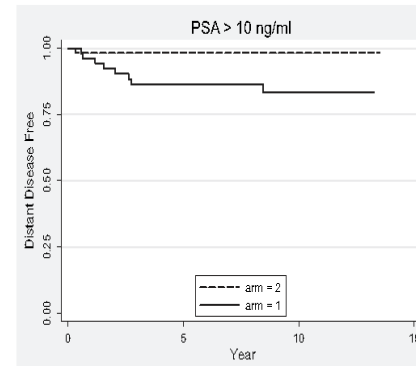
La RT doit utiliser une technique conformationnelle tridimensionnelle en modulation d'intensité (**IMRT**).

La RT guidée par l'image est nécessaire dès l'augmentation de dose au-dessus de 74Gy type **CBCT**

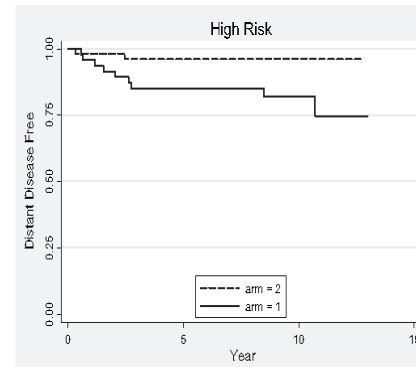


Prescription de dose

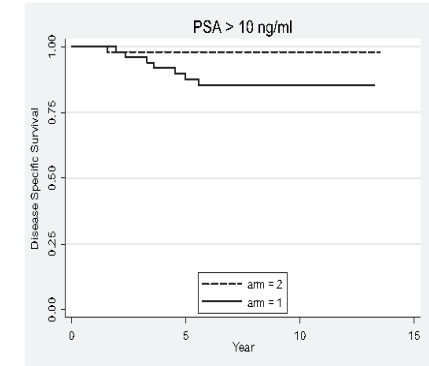
- L'augmentation de dose (76 à 80Gy) réalisée par RT externe, ou par curiethérapie
- Une amélioration significative du contrôle biochimique et de la survie sans récurrence clinique est rapportée ainsi que pour la survie spécifique, mais sans amélioration de la survie globale



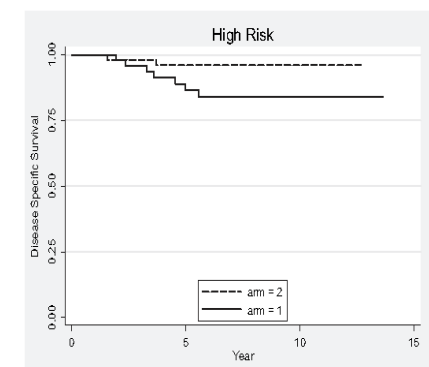
a.



b.



a.



b.

Fig. 5. Distant metastasis-free survival for patients with pretreatment prostate-specific antigen >10 ng/mL (a) and high-risk disease (b).

Fig. 6. Disease-specific survival for patients with pretreatment prostate-specific antigen >10 ng/mL (a) and high-risk disease (b).

Arm2: 78 Gy
Arm1: 70 Gy

Survie sans métastases

Survie spécifique

Volume d'irradiation

- Le volume initial comprend **la prostate** dans son ensemble.
- Il inclut également **les vésicules séminales** (le premier centimètre si vs non infiltrés)

Irradiation pelvienne

- Intérêt : analyse de la littérature

Pas d'arguments formels

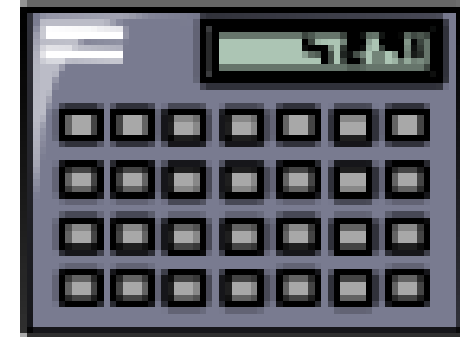
(Dirix, Radioth. Oncol., 2014)

Risque ganglionnaire

- Calcul du risque ganglionnaire :

$$\% \text{ LN+} = \frac{2}{3} (\text{PSA}) + (\text{GS}-6) \times 10$$

(Roach, IJROBP, 1993)



- Exemple: PSA: 24 ng/ml; Gleason: 7
 $\% \text{ LN+} = \frac{2}{3} (24) + (7 - 6) \times 10 = 16 + 10 = 26\%$

Quel cut-off pour la RT ganglionnaire?

Protocole RTOG 9410: résultats

| A 4 ans (%) | RT pelvis + prostate | RT prostate | P |
|------------------------|-------------------------|----------------|-------|
| Survie sans prog (PFS) | 54.2 | 47.0 | .022 |
| Survie | 84.7 | 84.3 | NS |
| Récidive ganglionnaire | 1.3 | 2.5 | 0.12 |
| Récidive biochimique | 33.5 | 39.7 | 0.065 |
| Métastases | 8.2 | 6.6 | NS |

PFS : échec local, gang. ou métast., échec biochimique,
décès quelque soit la cause

Pour notre patient

Nous avons réalisé une radiothérapie avec modulation d'intensité (**IMRT**)

séquentielle : - RT pelvienne

- RT prostate +vs

- RT prostate.

dose :78 gy

IGRT type CBCT quotidienne

- Hormonotherapie type

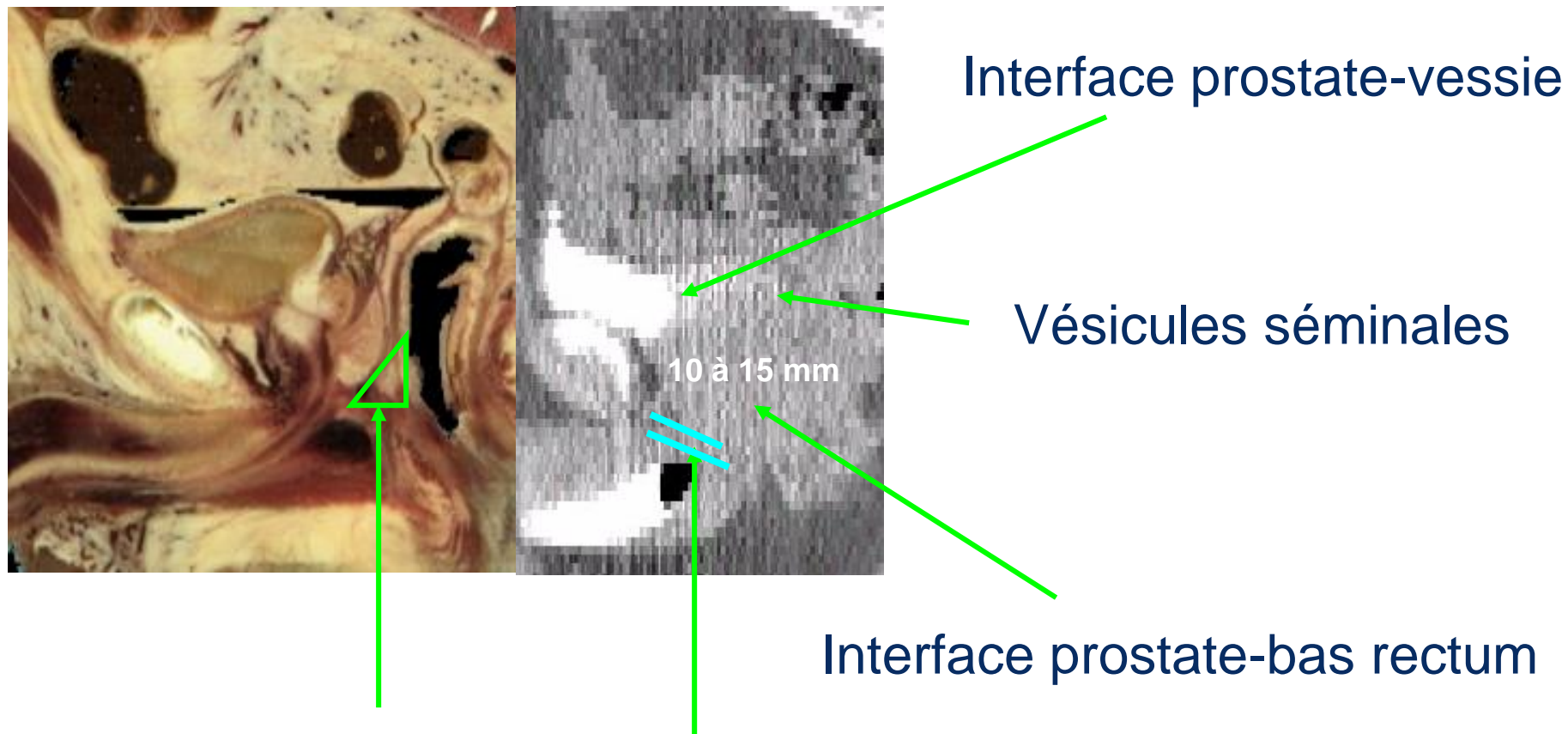
Les difficultés du contourage de la prostate

L'apex

La base

Les extensions extra-prostatiques

Zones de contour difficile : apex



Que préserver pour maintenir l'érection ?

Le bulbe pénien ?

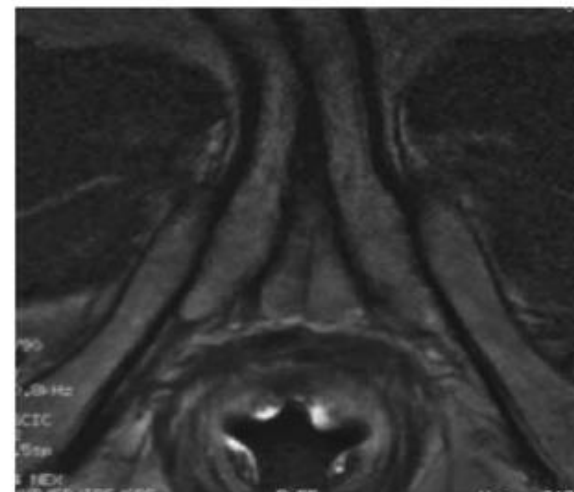
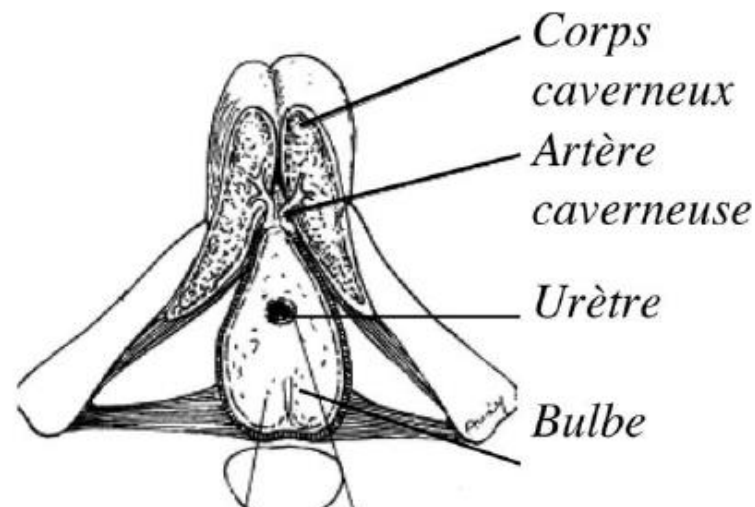
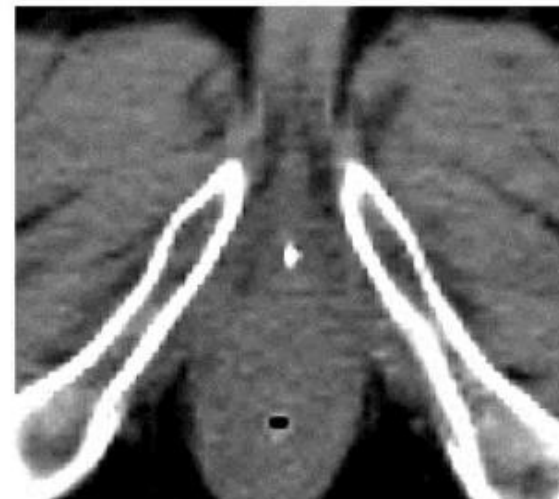
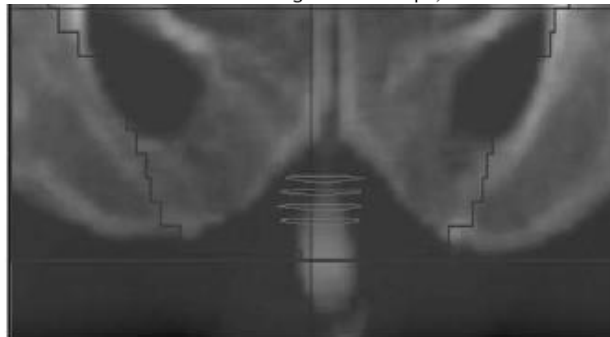
Les corps caverneux ?

Les artères pudendales ?

Zones de contour à protéger : le bulbe

Evaluating the relationship between erectile dysfunction and dose received by the penile bulb: Using data from a randomised controlled trial of conformal radiotherapy in prostate cancer (MRC RT01, ISRCTN4772397)

Stephen A. Mangar^a, Matthew R. Sydes^d, Helen L. Tucker^b, Jerome Coffey^a, Syed A. Sohaib^c, Stefano Gianolini^b, Steve Webb^b, Vincent S. Khoo^a, MRC RT01 Trial Management Group^d, David P. Dearnaley^{a,*}



Conclusion: There is evidence from this study to suggest a dose volume effect on the penile bulb and erectile dysfunction. A $D_{90} \geq 50$ Gy is associated with a significant risk of erectile dysfunction and this should form a basis for selecting dose constraints in future dose escalation studies.

Pour notre patient

- complications aiguës :
 - trouble digestif
 - trouble urinaire
- PSA nadir :0,02
- HT pdt 28 mois
- PSA de control :0,11
- Recul de :49 mois (mars 2018 – janvier 2022)

conclusion

- Les modalités de la prise en charge des patients doivent être définies sur la base des conclusions d'une réunion de concertation pluridisciplinaire
(RCP)
- Informer le patient est un devoir
- Le choix revient au patient
- Prise en charge des effets secondaires des traitements fait partie du traitement

Références

- [1] Leongamornlert D, Saunders E, Dadaev T, Tymrakiewicz M, Goh C, Jugurnauth-Little S, et al. Frequent germline dele- terious mutations in DNA repair genes in familial prostate cancer cases are associated with advanced disease. *Br J Can- cer* 2014;18(110):1663—72.
- [2] Xu J, Lange EM, Lu L, Zheng SL, Wang Z, Thibodeau SN, et al. HOXB13 is a susceptibility gene for prostate cancer: results from the International Consortium for Prostate Cancer Gene- tics (ICPCG). *Hum Genet* 2013;132(1):5—14.
- [3] Al Olama AA, Kote-Jarai Z, Berndt SI, Conti DV, Schumacher F, Han Y, et al. A meta-analysis of 87,040 individuals identi- fies 23 new susceptibility loci for prostate cancer. *Nat Genet* 2014;46(10):1103—9.
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