MRO. ART
INNOVATIVE TREATMENTS AND PATIENTS COMPLIANCE
31° RESIDENTIAL COURSE

Innovation, effectiveness and compliance in localized prostate cancer

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No specialty can claim the monopoly of the recovery of prostate cancer, to be considered as an act of solidarity and share where general practitionners, organ specialists, pathologists, urologists, radiation oncologists, medical oncologists and patients take part.

Plan

-Technical aspects

-Dose escalation

-EBRT with ADT

-Moderate and extreme Hypofractionation

-Low and high-dose rate Brachytherapy

- Brachytherapy boost

-Treatment intensification

-LHRH antagonists vs LHRH agonists

-Personalized treatment with genomic tests

-2021 EAU guidelines

EAU risk groups for biological recurrence of localized Prostate Cancer

European Association of Urology Guidelines 2021 edition

- Low risk : PSA < 10ng/mL and Gleason < 7 (ISUP grade 1) and cT1a-T2a

- Intermediate risk : PSA 10-20 ng/mL or Gleason 7 (ISUP grade 2/3) or cT2b

- High risk : PSA > 20 ng/mL or cT2c or Gleason > 7 (ISUP grade 4/5)

External beam radiotherapy : Technical aspects

- The treatment plan must conform to pre-specified dose constraints to organ at risk of normal tissue damage and a formal quality assurance process must be realized routinely.

- **Multicentric French study** to compare costs and clinical effectiveness and/or toxicity of Volumetric Modulated Arc Therapy (VMAT) and Helical tomotherapy (HT), techniques of rotational IMRT used in high-risk prostate cancer with pelvic irradiation.
- Data retrieved from the "RCMI pelvis" prospective multicenter study (NCT01325961) including 155 patients.
- Stabilized inverse probability of treatment weighting to assess the effects on total actual costs per patient and on toxicity

- Shorter treatment time and lower cost for VMAT

- Acute GI (p=0.21) and GU (p=0.42) toxicity more frequent in VMAT

- No difference in late toxicity up to 24 months after completion of treatment

Offer IMRT + IGRT for definitive treatment by external beam radiotherapy

(2021 EAU Guidelines : Strong strenght rating)

Dose escalation

(Kalbasi A. et al JAMA Oncol. 2015 ;1 (7): 897-906)

- Propensity matched retrospective analysis : US National Database
- 42.481 patients who received EBRT +/- ADT
- Low risk (n=12.229), Intermediate -risk (16.714), High-risk (13.358)
- Standard dose (68.4 – 75.6 Gy) vs escalated dose (75,6 - 90 Gy)
- Improved overall survival : Intermediate-risk ($P < 0.001$) and High-risk ($P < 0.001$)

High risk localized Prostate Cancer
Pelvic lymph-node irradiation

- There is no high level evidence for a prophylactic whole pelvic irradiation : the GETUG 01 and the RTOG 94-13 trials have shown no benefit on event-free survival or overall survival.

- Nevertheless, pelvic irradiation which was standard of care in the RCTs combining EBRT and ADT (RTOG 85-31, EORTC 22863, RTOG 92-02) must be done.

- The lymph-node CTV include external iliac, internal iliac, presacral, obturator and common iliac lymph-nodes with an upper border at the space L4/L5 (Lawton et al, Int J Radiat Oncol 2009) due to a high-risk of lymph-node failure with the space L5-S1 (Spratt et al Eur Urol 2017).

Neoadjuvant or adjuvant hormone therapy plus radiotherapy

- Long acting LHRH agonists delivered as depot injections on a 3-6 monthly basis

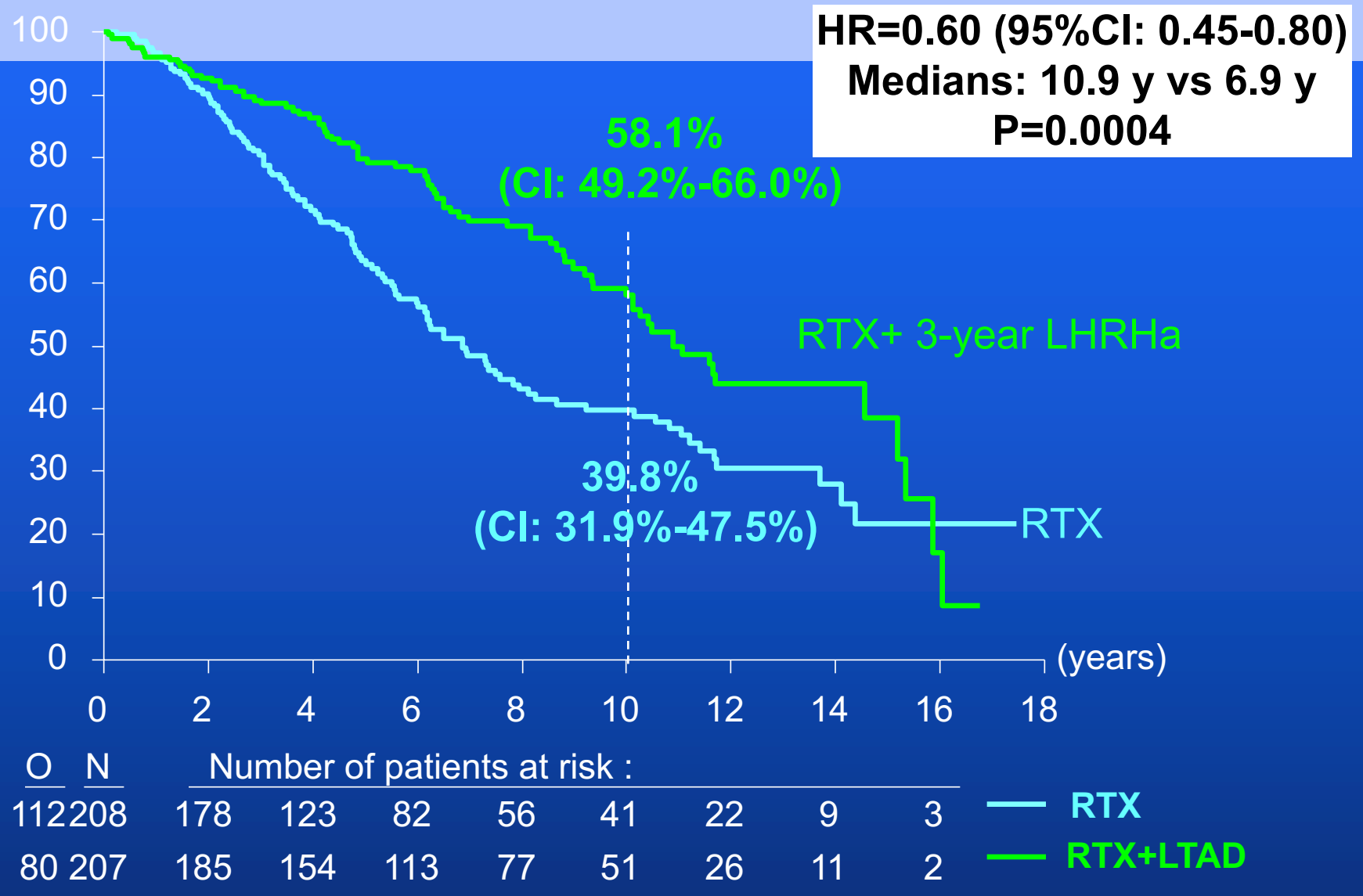
- Intermediate –risk : Short term ADT 6-month either neo-adjuvant or adjuvant

- High-risk : Long term ADT 2-3-year

EORTC 22863 10-year overall survival

415 patients T1-2 WHO grade 3, T3-4 N0-1 M0

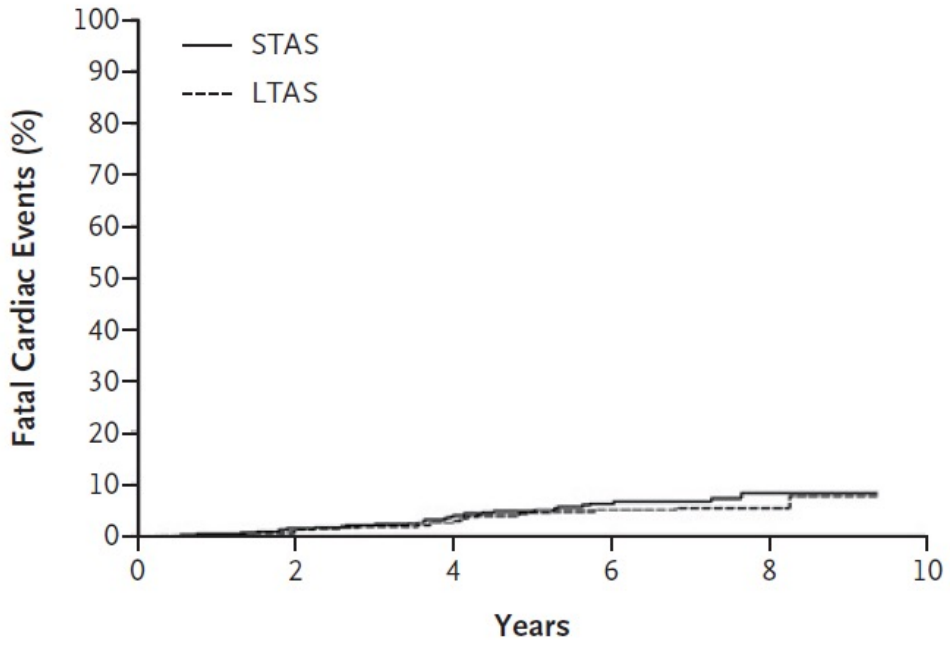
Bolla M. et al. Lancet Oncol 2010 ; 11 :1066-73



Androgen deprivation therapy: iatrogenic effects

- Anaemia
- Bone mineral density loss
- Fatigue
- Increase incidence of cardio-vascular mortality
- Modification of glucide and lipid metabolism
- Metabolic syndrome
- Neuro-degenerative illness
- Sexual side effects
- Weight gain

EORTC 22961 Cardiac event-specific mortality



No. at Risk						No. of Events
STAS	483	454	388	231	43	31
LTAS	487	454	407	249	50	25

Figure 3. Cumulative Mortality.

Panel A shows overall mortality and prostate-cancer–specific mortality, and Panel B shows cardiac-event–specific mortality. LTAS denotes long-term androgen suppression, and STAS short-term androgen suppression.

High-risk Prostate Cancer

Modulation of the duration of ADT

- To undertake a fruitful collaboration before, during treatment and follow-up with the general practitioner, the endocrinologist and the cardiologist. according to the patient co-morbidity

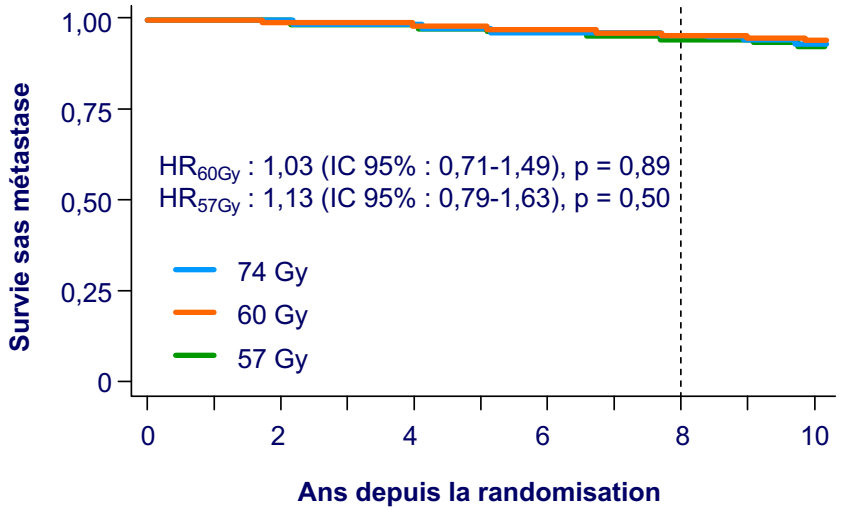
- Should there be a worrying cardiac co-morbidity don't hesitate to modulate the ADT duration (18 months)

- To wait for the results of RCTs comparing LHRH agonists and LHRH antagonists as regard overall survival and morbidity : EORTC trial 1414 with Dégarélix (B.Tombal, D. Bohmer)

CHHiP non inferiority trial

Low-risk (15%), intermediate (73%), high-risk (13%)

MDFS and overall survival 60 Gy = 74 Gy

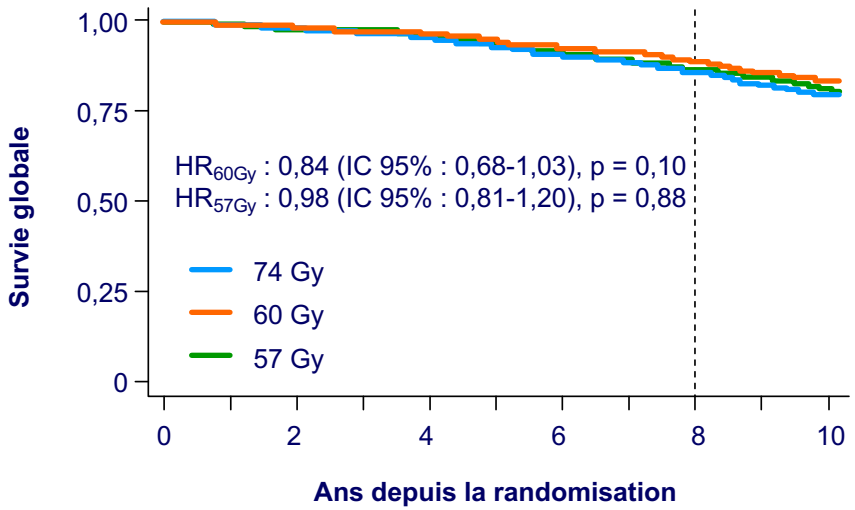


Patients à risque

74 Gy	1065 (1)	1025 (9)	984 (8)	897 (4)	710 (4)	305
60 Gy	1074 (1)	1039 (4)	1001 (10)	927 (11)	764 (2)	334
57 Gy	1077 (1)	1044 (8)	1001 (5)	920 (9)	739 (4)	322

Métastases à distance (n=176)
Survie sans évènement à 8 ans (%)

- 74 Gy : 95,6 % (IC 95% : 94,0-96,7)
- 60 Gy : 95,3 % (IC 95% : 93,7-96,4)
- 57 Gy : 94,8 % (IC 95% : 93,2-96,0)



Patients à risque

74 Gy	1065 (5)	1029 (11)	997 (26)	920 (24)	729 (21)	318
60 Gy	1074 (8)	1045 (11)	1014 (18)	949 (12)	793 (19)	349
57 Gy	1077 (8)	1049 (7)	1020 (22)	991 (22)	764 (15)	339

Décès (n=567)
Survie sans évènement à 8 ans (%)

- 74 Gy : 85,9 % (IC 95% : 83,6-97,9)
- 60 Gy : 88,6 % (IC 95% : 86,5-90,4)
- 57 Gy : 86,7 % (IC 95% : 84,5-88,7)

DP Dearnaley et al. ASCO GU 2020; abst 325

High-risk Prostate Cancer
Conventional vs moderate hypofractionation

(Niazi T. et al J Clin Oncol 2018; 36 (6) suppl 123)

- Multicentric Canadian phase III randomized trial
- 164 patients (conventional), 165 patients (moderate)
- Long-term ADT : 24-month median duration

- Conventional : Prostate = 76Gy/38 fr, pelvic LN (46 Gy)

- Moderate Prostate = 68 Gy (2.72 Gy/fr), pelvic LN = 45Gy/1.8Gy/fr

- Major end-point : toxicity grade ≥ 2 at 6 and 24 months

- Median follow-up : 40 months (24-60)

- No grade 4. 2-year GI toxicity (NS)

- 2-year GU toxicity in favor of hypofractionation (p=0.037)

Extreme Hypofractionation (>3.4 Gy/fx)

Jackson W.C. Int J Radiat Oncol Biol Phys 2019

- 6116 patients : LR (45%), IR (47%), HR (8%) ADT = 15%

- 4-7 fx, fx dose ≥ 5 gy

- Median follow-up : 39 months

- 5-year BRFS : 95.3% Estimated late ≥ 3 GU toxicity GU (2%) GI (1.1%)

- To restrict extreme hypofractionation to prospective clinical trials and to inform patients on the uncertainties of long term outcomes (*2021 EAU Guidelines*)

Extreme Hypofractionation (> 3.4 Gy/fx)

Health Related Quality of Life

- EPIC-26 : 3293 patients

- Urinary and bowel score returned to baseline by 2-year post-TTT and remained non-significantly different to 5-year post SBRT

- Sexual domain score gradually decreased over time not reaching statistical significance until 3 years post SBRT

Low dose rate brachytherapy

Permanent implanted 125-iodine seeds

- T1b-2a N0 M0, PSA ≤ 10 ng, prostate volume ≤ 50ml

-IPSS ≤ 12, maximal flow rate > 15 mL

- ISUP 1 < 50% cores +, ISUP 2 < 33% cores +

(Bolla M. et al Cancer Radiother. 2014. 18:643-6)

- 200 cases (2001-2011) T1c (79.5%) T2a-b (20.5%)
- LR (83.5%), IR (16.5%)
- D90 > 140 Gy
- Median F-U : 69 months (16-135)

-10-year BRFS : 89.7 % (C.I. 95% 79.4-95) 10-year DSS : 99.1 % (C.I. 95% 93-99.9)

-10-year grade 3 late GU toxicity : 4% (C.I. 95% 2-5.9)

Offer LDR brachytherapy monotherapy to patients with good urinary function and low or good prognosis intermediate-risk localized disease (*2021 EAU Guidelines*)

Multi-fraction High dose rate Brachytherapy

Low and intermediate-risk disease

(Morton G et al. Radiother Oncol 2020; 146:90-96)

- 170 patients : 2 fractions (total 27 Gy) or single 19 Gy HDR-BT monotherapy

- Median F-U : 51 months

- BDFS : 97.3% vs 74.5%

- Data consistant with other studies using multi-fraction HDR-BT monotherapy which have consistently shown 5-year PSA control rate over 90%, late grade 3+ GU toxicity < 5% , and very minimal grade 3+ GI toxicity

- Fractionated brachytherapy, as monotherapy can be offered to patients with low or intermediate risk who should be informed that results are only available from limited series.

ASCENDE –RT trial : intermediate and high risk patients

LDR brachytherapy boost vs dose escalated EBRT boost

(Rodda et al. Int J Radiat Oncol Biol Phys 2015 ; 93 :S121)

- ADT : 12 months
- EBRT (46 +32 Gy) vs EBRT (46 Gy + 115 Gy LDR)
- Median Follow-up : 6.5 years

- 7-year BRFS : 75 % vs 86% ($p<0.004$), OS ($p = 0.62$)

- 5-year cumulative grade 3 toxicity : LDR boost (19%) vs 5% (EBRT)

- negative impact on HRQoL for urinary and sexual function, general health and bodily pain

- **Offer LDR or HDR brachytherapy boost combined with IMRT including IGRT to patients with good urinary function and intermediate risk with adverse features, or high-risk disease** *(Strong strenght rating 2021 EAU Guidelines)*

Androgen deprivation therapy Intensification

PROSTATE

RCT	Eligibility	Control Arm	Experimental arm	Major end-point
ENZARAD NCT02446444	High-risk localized PCa	EBRT + ADT(2 yrs) NSAA (6 months)	EBRT + ADT Enzalutamide (2 years)	MDFS*
ATLAS NCT02531516	High-risk localized PCa	EBRT+ADT (30 months) + Bicalutamide (4 months)	EBRT + ADT Apalutamide (30 months)	MDFS
STAMPEDE NCT00268476	High-risk localized PCa	RT + HT (2 ans)	EBRT+ ADT Abiratérone (2 years)	OS

- **Results not yet published**

SS Sridhar et al. ASCO GU 2019

High-Risk Prostate Cancer : Adjuvant Chemotherapy

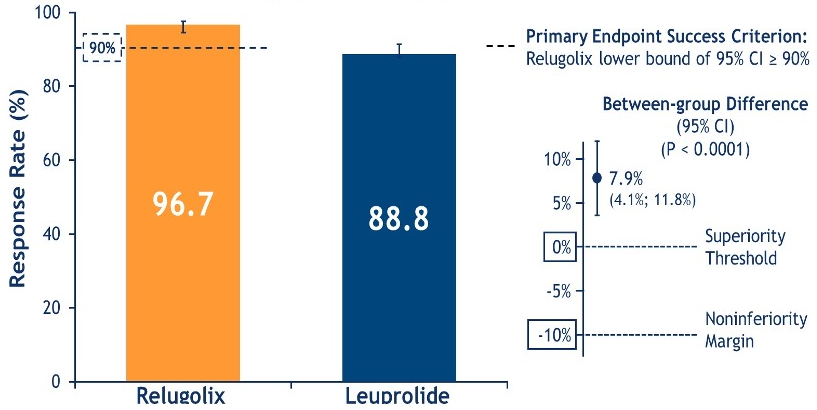
		n	F-U	T3/4	GI 8-10	M1	OS	DFS
RTOG 99020	IJROBP 2015	380	9,2 yrs	34 %	68 %	16 % 14 %	63 % 65 %	10-year HR : 0,9 22 vs 25,8 %
GETUG*12	Lancet 2015	413	8,8	68 %	42 %	20 % 15 %	83 %	8-year HR : 0,71 50 vs 62 %*
STAMPEDE	Lancet 2016	697/2962	3,5	70 %	82 %	Not reported	Nr	HR : 0,6
RTOG 0521	JCO 2019	563	5,7	27 %	53 %	14 % 9 %	89 % 93 %	6-year HR:0,76 55 vs 65 %

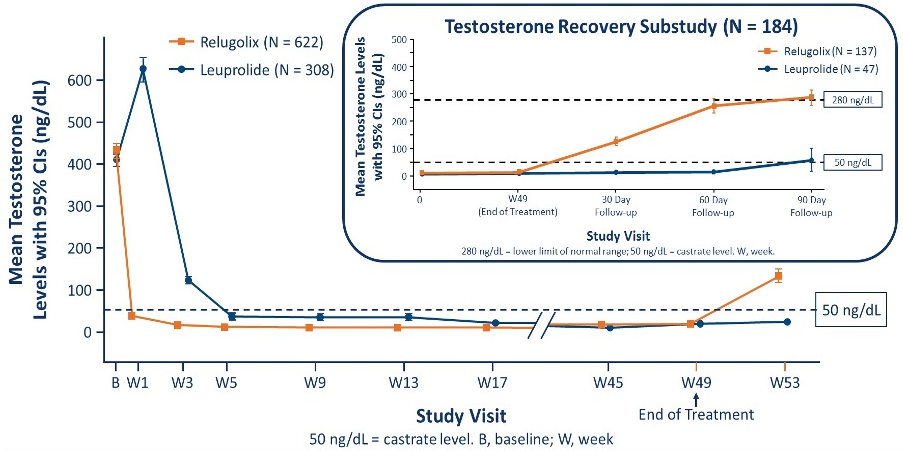
No room for adjuvant chemotherapy

JM Crook. ASCO GU 2020

HERO – Relugolix, antagoniste de la GnRH, oral

- **Efficacité :**
  - 96,7% de castration à la semaine 48
  - Supérieure au leuprolide en :
    - Taux de réponse psa (j15)
    - Taux de castration profonde à J15
    - Récupération de testostéronémie rapide à l'arrêt à J90 : 54% (R) vs 3% (L)



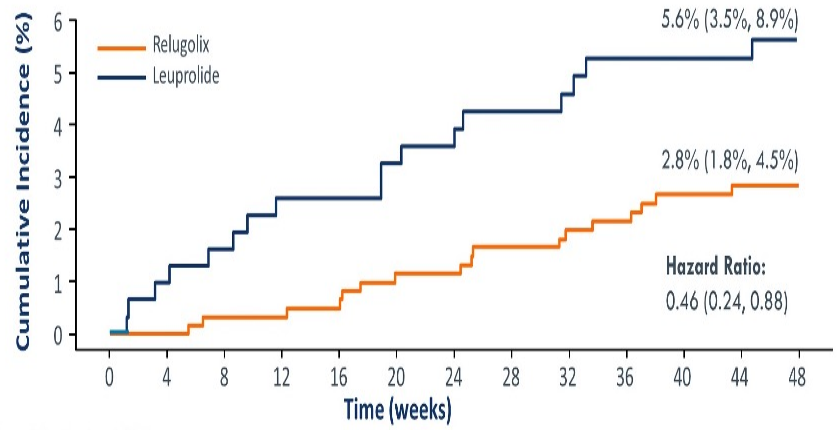


Shore N et al. ASCO® 2020; Abstr 5602; Shore N et al. New Engl J Med 2010

HERO – Relugolix, antagoniste de la GnRH, oral

- **Tolérance**:
  - Effets II reliés au tt pour 73,6% (R) versus 68,8% (L)
  - FDR cardiovasculaires à l'inclusion: 91,6% (R) vs 94,2% (L)
  - Réduction Significative de 54% du risque de complications cardiovasculaires sévères (IDM, mortalité toute cause, accident cérébral)
  - Nouvel antagoniste de la GnRH

Incidence complications cardiovasculaires



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

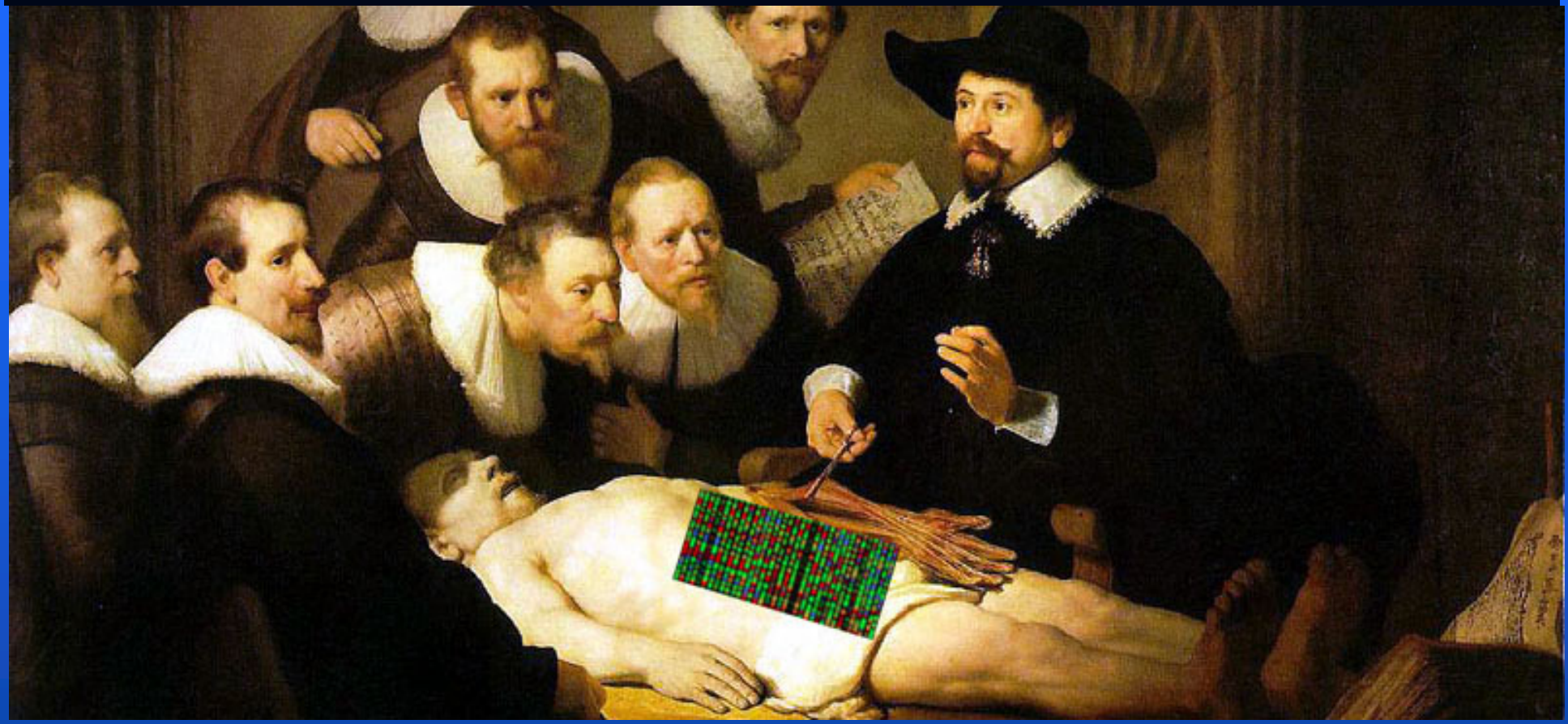
Oral Relugolix for Androgen-Deprivation Therapy in Advanced Prostate Cancer

History of MACE	Yes		No	
N (%)	Relugolix 84 (13.5%)	Leuprolide 45 (14.6%)	Relugolix 538 (86.5%)	Leuprolide 263 (85.4%)
MACE	3.6%	17.8%	2.8%	4.2%
Odds Ratio Leuprolide vs Relugolix (95% confidence interval)	5.8 (1.5, 23.3)		1.5 (0.7, 3.4)	

MACE = non-fatal myocardial infarction + non-fatal stroke + all-cause mortality

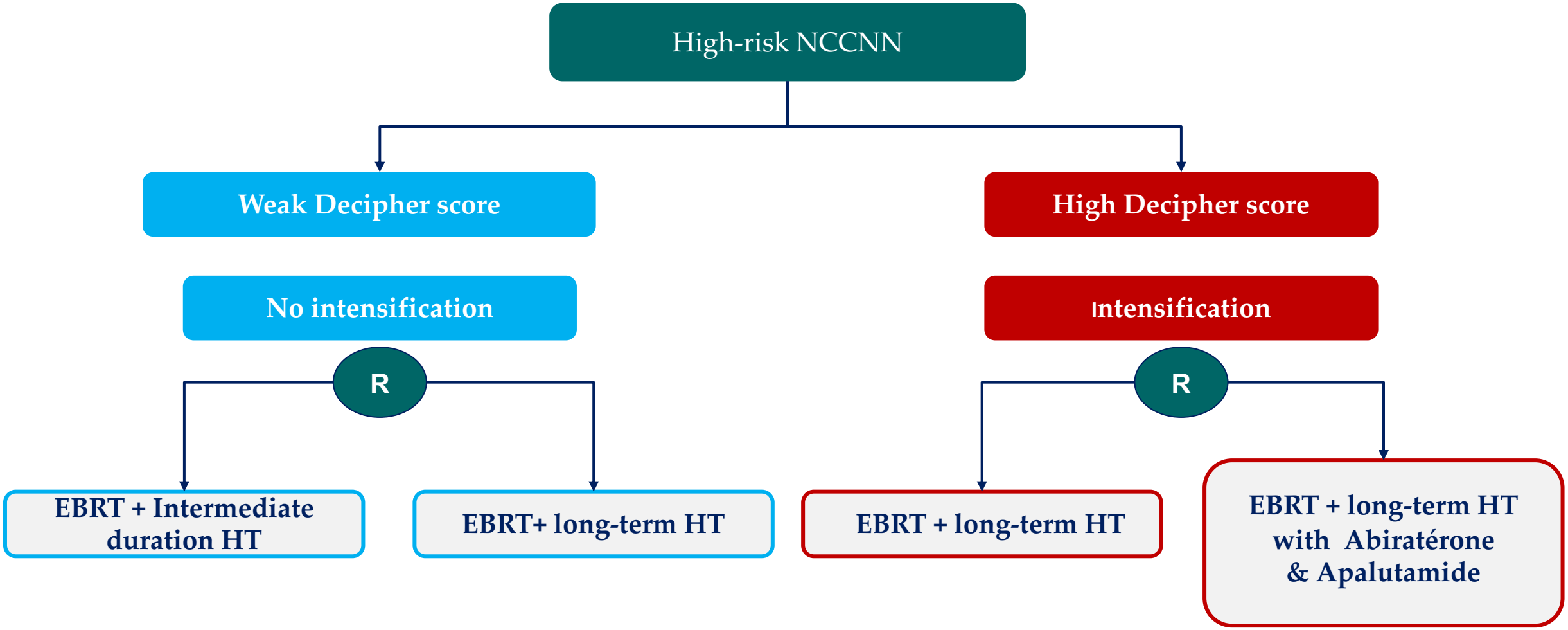
Shore N et al. ASCO® 2020; Abstr 5602; Shore N et al. New Engl J Med 2010

Genomic prognostic biomarkers



Prolaris, Oncotype Dx and Decipher tests.

Genomic Prognostic Biomarker (NRG GU 1864 Trial)



Feng FY et al. ASCO GU 2019

Low risk Prostate Cancer

2021 EAU guidelines

- Offer low dose rate brachytherapy to patients without a recent transurethral resection of the prostate and a good International Prostatic Symptome Score *(Strong strenght rating)*

- Use intensity-modulated radiation therapy plus image guided radiation therapy with a total dose of 74-80 Gy or moderate hypofractionation (60 Gy/20 fx in 4 weeks or 70 Gy / 28 fx in 6 weeks) without androgen deprivation therapy *(Strong strenght rating)*

Intermediate risk Prostate Cancer

2021 EAU guidelines

- Offer low dose rate brachytherapy to intermediate-risk patients with ISUP grade 2 with ≤ 33% of biopsies cores involved without a recent transurethral resection of the prostate and with a good International Prostatic Symptome Score *(Strong strenght rating)*

- For intensity-modulated radiation therapy plus image guided radiation therapy use 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 combinaison with short term androgen deprivation therapy (4 to 6 months) *(Strong strenght rating)*

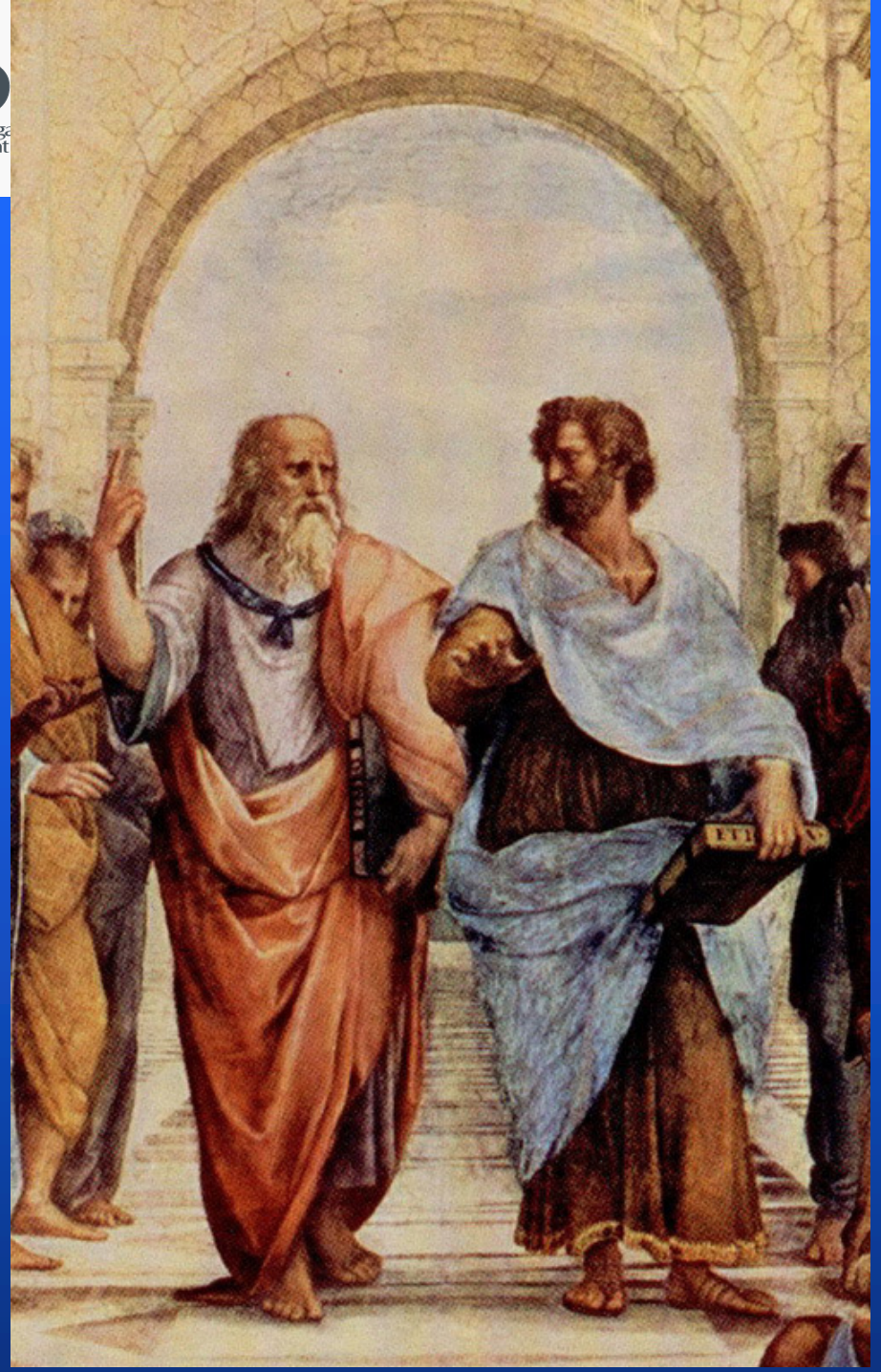
- In patients not willing to undergo ADT use a total dose of IMRT plus IGRT of 76-78 Gy or moderate hypofractionation or a combination with brachytherapy *(Weak strenght rating)*

High-risk Prostate cancer

2021 EAU guidelines

- In patients with high-risk localized disease use intensity-modulated radiation therapy (IMRT) plus image guided radiation therapy (IGRT) with 76-78 Gy in combination with 2-3 year ADT *(Strong strenght rating)*

- In patients with high-risk-risk localized disease use IMRT with IGRT plus brachytherapy boost (either HDR or LDR ate) in combination with 2-3 year ADT *(Strong strenght rating)*



Per concludere, conviene sottolineare che al di là della concertazione pluridisciplinare e delle techniche sempre più sofisticate, non è da dimenticare l'importanza della relazione "medico-paziente",in cui interviene il radioterapista con l'ascolto e con l'empatia, allo scopo di offrire ai pazienti un'informazione terapeutica insieme colla sperenza di guarigione e del mantenimento della qualità di vita