XXXIII CONGRESSO NAZIONALE AIRO

AIRO2023

BOLOGNA,
27-29 OTTOBRE 2023
PALAZZO DEI CONGRESSI

Radioterapia Oncologica: l'evoluzione al servizio dei pazienti

La terapia con farmaci ormonali nel paziente con carcinoma della prostata

Davide Tomasini, MD

Istituto del Radio O.Alberti,
Spedali Civili Brescia
Università degli Studi di Brescia

Associazione Italiana
Radioterapia e Oncologia clinica

ROAD MAP

- Androgen Deprivation Therapy: several drugs
- Radiobiological rational RT + ADT
- Radiotherapy + ADT: when
- Theory in clinical practice

ANDROGEN DEPRIVATION THERAPIES

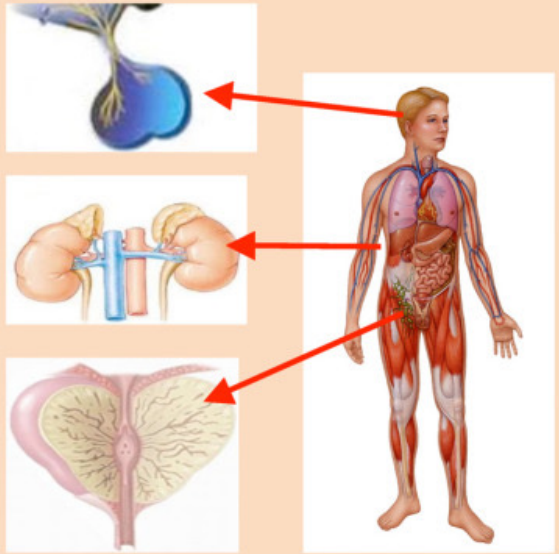
Leuprolide, triptorelin, goserelin

Degarelix, relugolix

Abiraterone

Bicalutamide, flutamide, nilutamide
Or
Enzalutamide, apalutamide, darolutamide

Class of Drugs	Region of Action	Mechanism of Action
GnRH Agonists	Anterior pituitary gland	Decrease release of LH through downregulation of GnRH receptors
GnRH Antagonists	Anterior pituitary gland	Direct inhibition of GnRH receptors
Adrenal Ablating Drugs	Adrenal gland	Decrease androgen synthesis from steroid precursors through inhibition of cytochrome P450 enzymes
Androgen Receptor Antagonists	Prostate	Through competitive binding, inhibition of androgen receptor ligand-binding domain

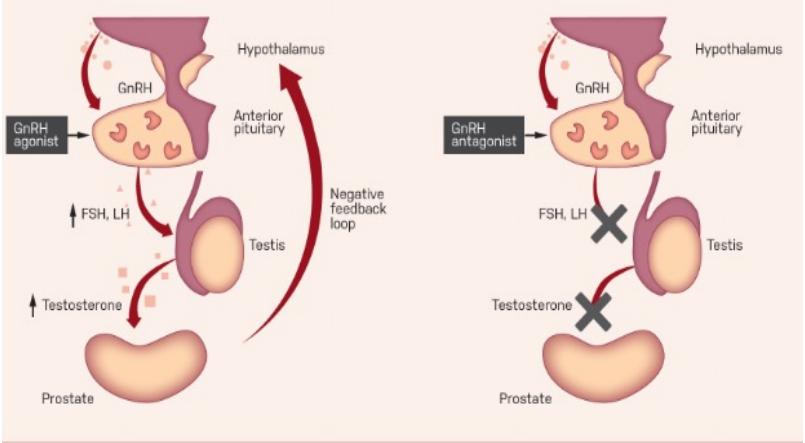


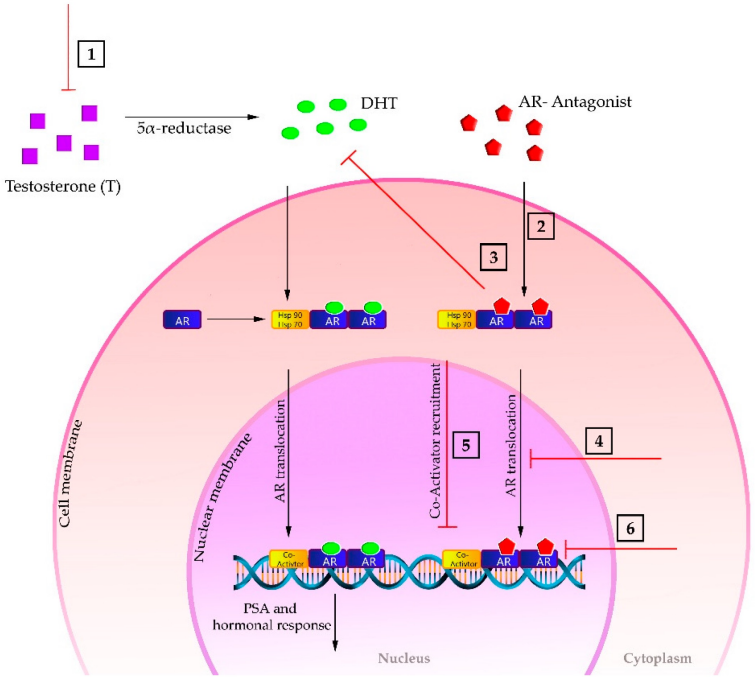
GnRH AGONISTS/ANTAGONISTS

- **GnRH-agonists** overstimulate GnRH receptors leading to downregulation of pituitary receptors, inhibition of LH and FSH release, and a concurrent reduction in testosterone production. With time, overstimulation leads to desensitization and production of LH, FSH, and testosterone is reduced

  → GnRH-agonists stimulate testosterone production before shutting it down (*flare*) for the first 30 days.

- **GnRH-antagonists** inhibit testosterone production directly (competitive inhibition of pituitary GnRH receptors). This blockade directly suppresses the secretion of LH and FSH and thereby reduces testosterone production





1. Suppresses testosterone production
- Surgical and Medical Castration Therapy
- Abiraterone acetate

2. Competitive binding to AR
- Bicalutamide*
- Enzalutamide
- Apalutamide
- Darolutamide

3. Prevents DHT-AR binding
- Bicalutamide*
- Enzalutamide
- Apalutamide
- Darolutamide

4. Blocks AR translocation to nucleus
- Enzalutamide
- Apalutamide
- Darolutamide

5. Impairs Co-Activator recruitment
- Enzalutamide
- Apalutamide
- Darolutamide

6. Restrains AR-DNA binding
- Enzalutamide
- Apalutamide
- Darolutamide

*First generation nonsteroidal AR antagonist

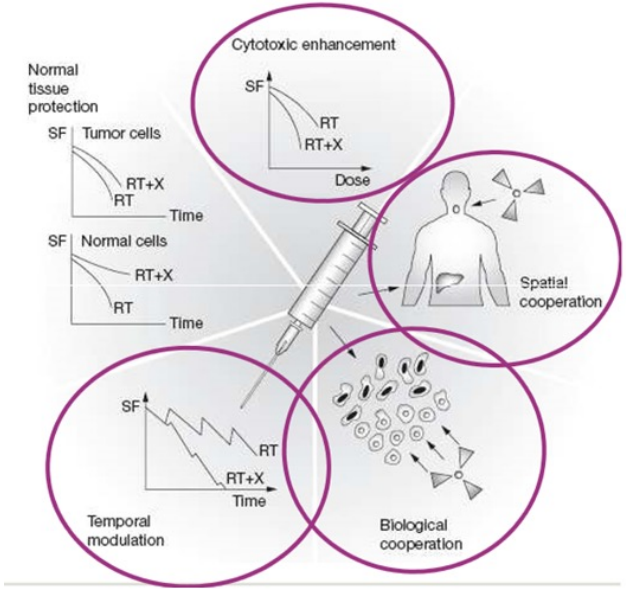
AR ANTAGONISTS

- Competitive binding to AR and DHT-AR binding prevention are typical for both 1° and 2° generation AR antagonists
- 2° generation AR antagonists share further and peculiar charachteristics
- 2° generation AR antagonists also inhibit the AR translocation from cytoplasm to cell nucleus, the coactivator recruitment, and the AR-DNA binding.

Prostate cancer cell proliferation and survival

RADIOBIOLOGICAL RATIONAL RT+ADT

- Spatial cooperation
- Normal tissue protection
- Cytotoxic enhancement
- Biological cooperation
- Temporal modulation



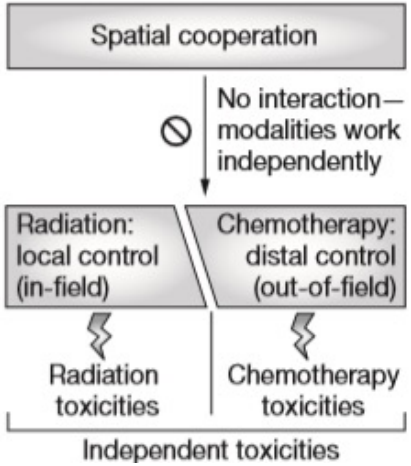
Steel, Peckham 1997
Bentez SM 2007

SPATIAL COOPERATION

Definition: describe the scenario whereby RT acts loco regionally, and drugs (ADT, CHT) acts against distant micro metastases, without interaction between the agents

↓

ADT represents a keystone in PC



RADIOBIOLOGICAL RATIONAL RT+ADT

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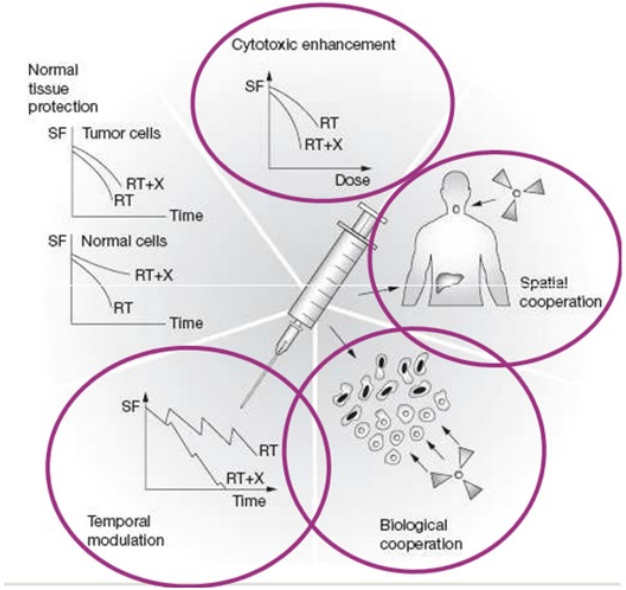


Steel, Peckham 1997
Bentez SM 2007

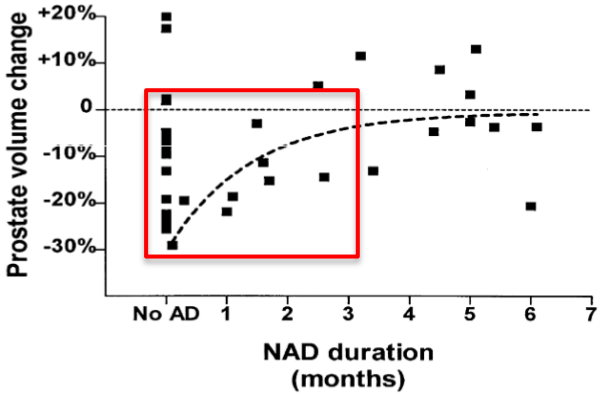
NORMAL TISSUE PROTECTION

Neoadjuvant ADT: downsizing in prostate volume

Table 1. Baseline characteristics and parameter changes of 110 patients after androgen deprivation therapy

Variable	Baseline	After ADT	P-value
PSA (ng/mL)	64.89 ± 21.15*	8.01 ± 3.17	< 0.01
Prostate volume (mL)	36.65 ± 14.59*	19.49 ± 12.47	< 0.01

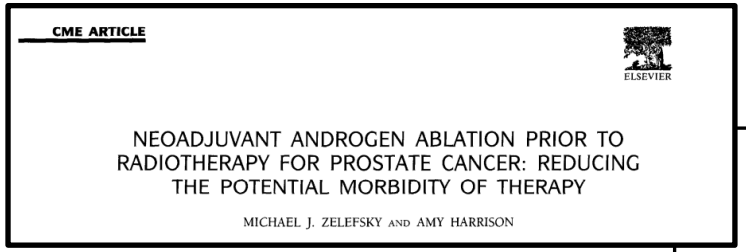
"…ADT resulted in statistically significant clinical improvement in terms of prostate volume…when analyzed by ADT duration and prostate volume…"



Sanguineti G, et al 2003
Choi H, et al 2016

NORMAL TISSUE PROTECTION

Neoadjuvant ADT: downsizing in prostate volume

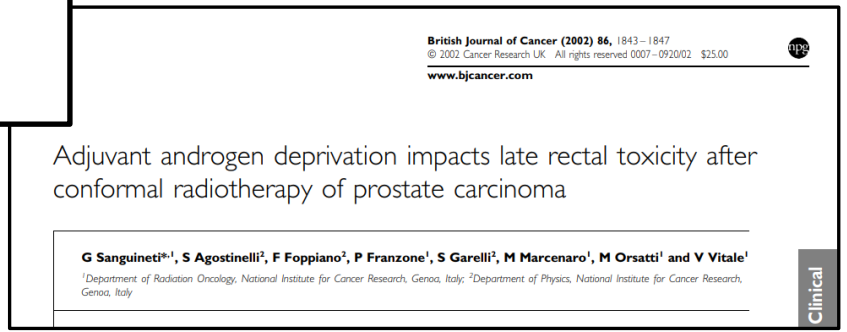


CME ARTICLE

ELSEVIER

NEOADJUVANT ANDROGEN ABLATION PRIOR TO RADIOTHERAPY FOR PROSTATE CANCER: REDUCING THE POTENTIAL MORBIDITY OF THERAPY

MICHAEL J. ZELEFSKY AND AMY HARRISON



British Journal of Cancer (2002) 86, 1843 – 1847
© 2002 Cancer Research UK All rights reserved 0007 – 0920/02 $25.00
www.bjcancer.com

Adjuvant androgen deprivation impacts late rectal toxicity after conformal radiotherapy of prostate carcinoma

G Sanguineti*,[1], S Agostinelli[2], F Foppiano[2], P Franzone[1], S Garelli[2], M Marcenaro[1], M Orsatti[1] and V Vitale[1]

[1]Department of Radiation Oncology, National Institute for Cancer Research, Genoa, Italy; [2]Department of Physics, National Institute for Cancer Research, Genoa, Italy

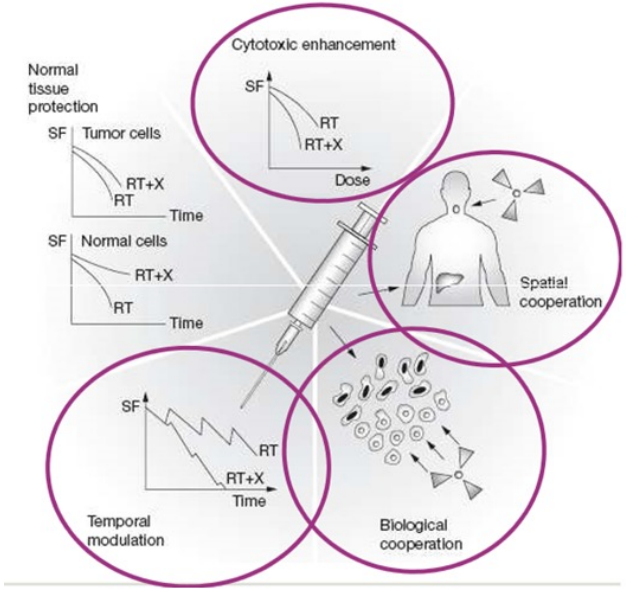
Clinical

"…Our results show that rectal tolerance is reduced in presence of hormonal therapy…The underlying mechanism of such phenomenon is not known…The fact that neoadjuvant AD has little impact on late rectal toxicity compared to adjuvant AD suggests that AD may hamper the reparative process of the rectal tissue that is damaged by radiotherapy.."

Sanguineti G, et al 2003
Zelefsky M 1997

RADIOBIOLOGICAL RATIONAL RT+ADT

- Spatial cooperation ✓
- Normal tissue protection ≈
- Cytotoxic enhancement
- Biological cooperation
- Temporal modulation



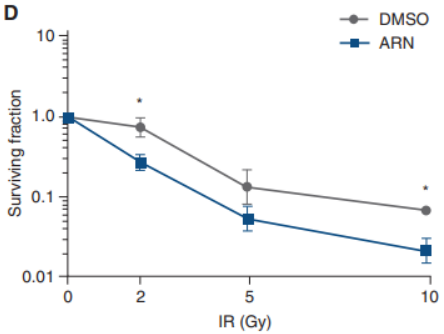
Steel, Peckham 1997
Bentez SM 2007

CYTOTOXIC ENHANCEMENT

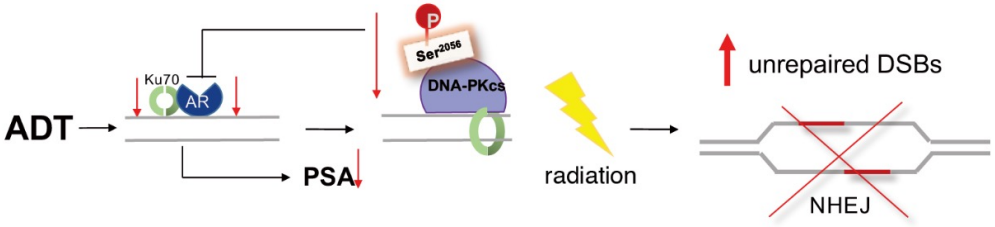
Definition: …combination of therapies that leads to an interaction on some level that generates an improved antitumor effect relative to each treatment alone

- Exacerbation of DNA Damage
- Inhibition of DNA Repair
- Cell Cycle Effects
- Enhanced Apoptosis
- Targeted Radiosensitizers

ADT + RT FOR PC: A THERAPEUTIC SYNERGY?



"…prostate cancer cells treated with IR plus androgen demonstrate enhanced DNA repair and decreased DNA damage and furthermore that antiandrogen treatment causes increased DNA damage and decreased clonogenic survival…"



Polkinghorn WR et al, 2013

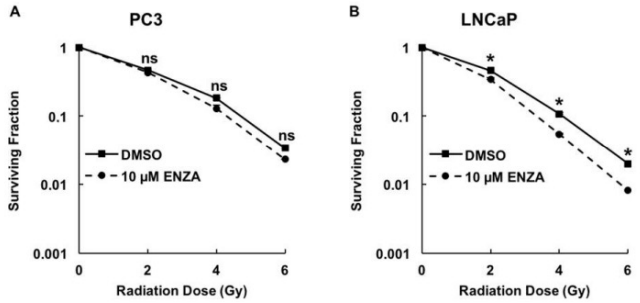
ADT + RT FOR PC: A THERAPEUTIC SYNERGY?

ANTICANCER RESEARCH *38*: 3487-3492 (2018)
doi:10.21873/anticanres.12619

Exploring the Role of Enzalutamide in Combination with Radiation Therapy: An *In Vitro* Study

LUCA TRIGGIANI[1], ANTONELLA COLOSINI[1], MICHELA BUGLIONE[1], NADIA PASINETTI[1], FLAVIA ORIZIO[2], LILIA BARDOSCIA[1], PAOLO BORGHETTI[1], MARTA MADDALO[1], LUIGI SPIAZZI[3], STEFANO MARIA MAGRINI[1] and ROBERTO BRESCIANI[2]

[1]*Department of Radiation Oncology, University and Spedali Civili Hospital, Brescia, Italy;*
[2]*Department of Molecular and Translational Medicine, Unit of Biotechnology, University of Brescia, Brescia, Italy;*
[3]*Medical Physics Department, Spedali Civili Hospital, Brescia, Italy*

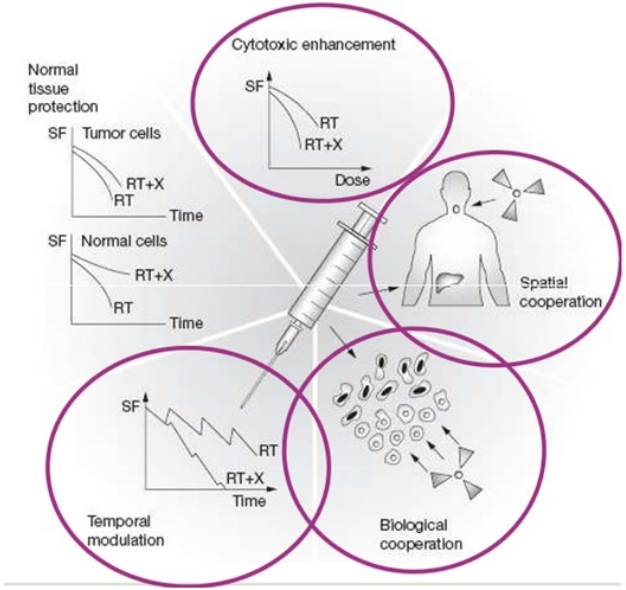


"..The combination of enzalutamide with ionizing radiation significantly improves radio-sensitivity of hormone-dependent LNCaP cells.."

Triggiani et al, 2018

RADIOBIOLOGICAL RATIONAL RT+ADT

- Spatial cooperation ✓
- Normal tissue protection ≈
- Cytotoxic enhancement ✓
- Biological cooperation
- Temporal modulation



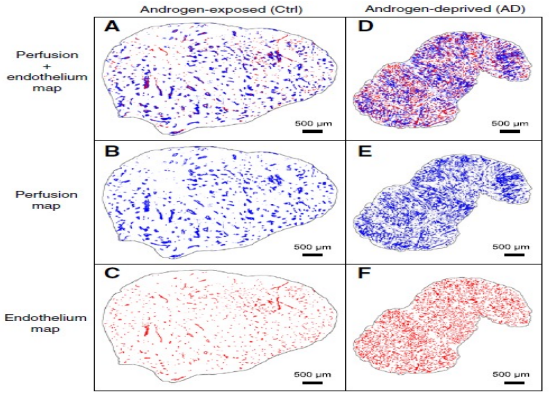
Steel, Peckham 1997
Bentez SM 2007

BIOLOGICAL COOPERATION

Definition: this is the second of the mechanisms of radiosensitization and refers to strategies that:

- Target distinct cell populations
- Employ different mechanisms for cell killing
- Delaying tumor regrowth

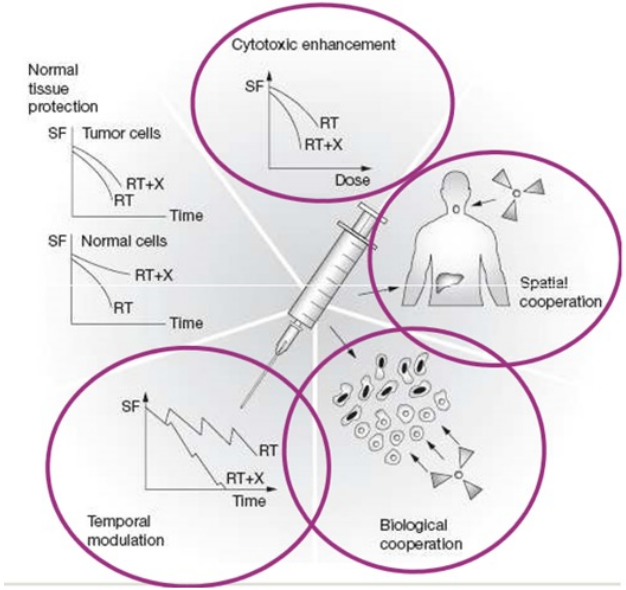
N.B: the cells targeted are not necessarily the malignant cells only



Vascular responses to radiotherapy and androgen-deprivation therapy in experimental prostate cancer.

RADIOBIOLOGICAL RATIONAL RT+ADT

- Spatial cooperation ✓
- Normal tissue protection ≈
- Cytotoxic enhancement ✓
- Biological cooperation ✓
- Temporal modulation



Steel, Peckham 1997
Bentez SM 2007

TEMPORAL MODULATION

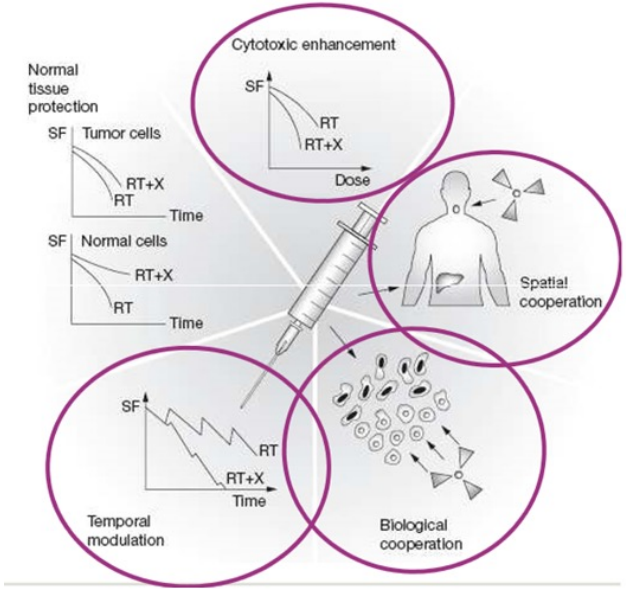
- The aim of this approach is to enhance the tumor response to fractionated radiotherapy.
- The four R's of radiotherapy:
  1. Repair → DNA damage repair
  2. Repopulation → cellular repopulation or proliferation
  3. Reoxygenation → reoxygenation of hypoxic tumor cells
  4. Redistribution → redistribution to more sensitive phases of the cell cycle

→ SBRT?

For example: radioenhancing drugs in this context could function by inhibiting repair taking place between dose fractions.

RADIOBIOLOGICAL RATIONAL RT+ADT

- Spatial cooperation ✓
- Normal tissue protection ≈
- Cytotoxic enhancement ✓
- Biological cooperation ✓
- Temporal modulation ✓



Steel, Peckham 1997
Bentez SM 2007

RADIOTHERAPY + ADT: WHEN?

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2023
Prostate Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF RADIATION THERAPY

Definitive Radiation Therapy by Risk Group

- Very low risk
  - Patients with NCCN very-low-risk prostate cancer are encouraged to pursue active surveillance.
- Low risk
  - Patients with NCCN low-risk prostate cancer are encouraged to pursue active surveillance.
  - Prophylactic lymph node radiation should NOT be performed routinely. ADT or antiandrogen therapy should NOT be used routinely.
- Favorable intermediate risk[a]
  - Prophylactic lymph node radiation is not performed routinely, and ADT or antiandrogen therapy is not used routinely. Prophylactic lymph node radiation and/or ADT use is reasonable if additional risk assessments suggest aggressive tumor behavior.
- Unfavorable intermediate risk[a]
  - Prophylactic nodal radiation can be considered if additional risk assessments suggest aggressive tumor behavior. ADT should be used unless additional risk assessments suggest less-aggressive tumor behavior or if medically contraindicated. The duration of ADT can be reduced when combined with EBRT and brachytherapy. Brachytherapy combined with ADT (without EBRT), or SBRT combined with ADT can be considered if delivering longer courses of EBRT would present medical or social hardship.
- High and very high risk[a]
  - Prophylactic nodal radiation should be considered. ADT is required unless medically contraindicated. Brachytherapy combined with ADT (without EBRT), or SBRT combined with ADT, can be considered if delivering longer courses of EBRT would present a medical or social hardship.
- Regional disease
  - Nodal radiation should be performed. Clinically positive nodes should be dose-escalated as dose-volume histogram parameters allow. ADT is required unless medically contraindicated, and the addition of abiraterone or fine-particle abiraterone (category 2B) to ADT is preferred.
- Low metastatic burde… …disease
  - RT to the p… …metastatic burden… …cont… …me…
- Low… …nph-nod… …eral/ other…
  - ◊ Num… …itional imaging.
  - ◊ At this time, meta… …PET imaging should not be used to exclude a patient from treatment of the primary tumor.
- This recommendation is based on the STAMPEDE phase 3 randomized trial, which randomized 2061 patients to standard systemic therapy with or without radiotherapy to the primary. The overall cohort had a significant improvement from the addition of radiotherapy to the primary in failure-free survival, but not overall survival. The prespecified low-volume subset had a significant improvement in both failure-free survival and overall survival.[1] A meta-analysis with two other studies confirmed this benefit for primary RT to the primary tumor in lower volume disease.[2]

HOW DID WE GET HERE?

NCCN, 2023

RADIOTHERAPY + ADT IN INTERMEDIATE RISK PC

The **DFCI 95-096** and the **RTOG 9408** randomized controlled trials established the known benefit of 4 to 6 months of ADT in IR disease

DFCI 95-096 trial (D'Amico JAMA 2008):

- 206 men with cT1b-T2b disease (75% intermediate-risk) to 70 Gy RT with or without 6 months of ADT.
- Significant OS advantage with ADT at median FU of 8 years: 74% vs 61%, p= 0.01.
- Post hoc analysis (2011) confirmed an OS benefit with ADT for patients with intermediate-risk disease and no or minimal comorbidity (AHR = 3.0, 95% CI: 1.3−7.2, P = 0.01)

INSUFFICIENT DOSES!!!

The RTOG 9408 trial
(Jones C. N Engl J Med 2011)

- 1,979 pts with cT1b-T2b disease (34.6% low-risk, 54.0% intermediate-risk, 11.4% high-risk) to 66.6 Gy with or without 4 months of ADT .
- FU of 9.1 years, RT with ADT had significantly higher OS: 62% vs 57%, p= 0.01 only for patients with intermediate-risk disease

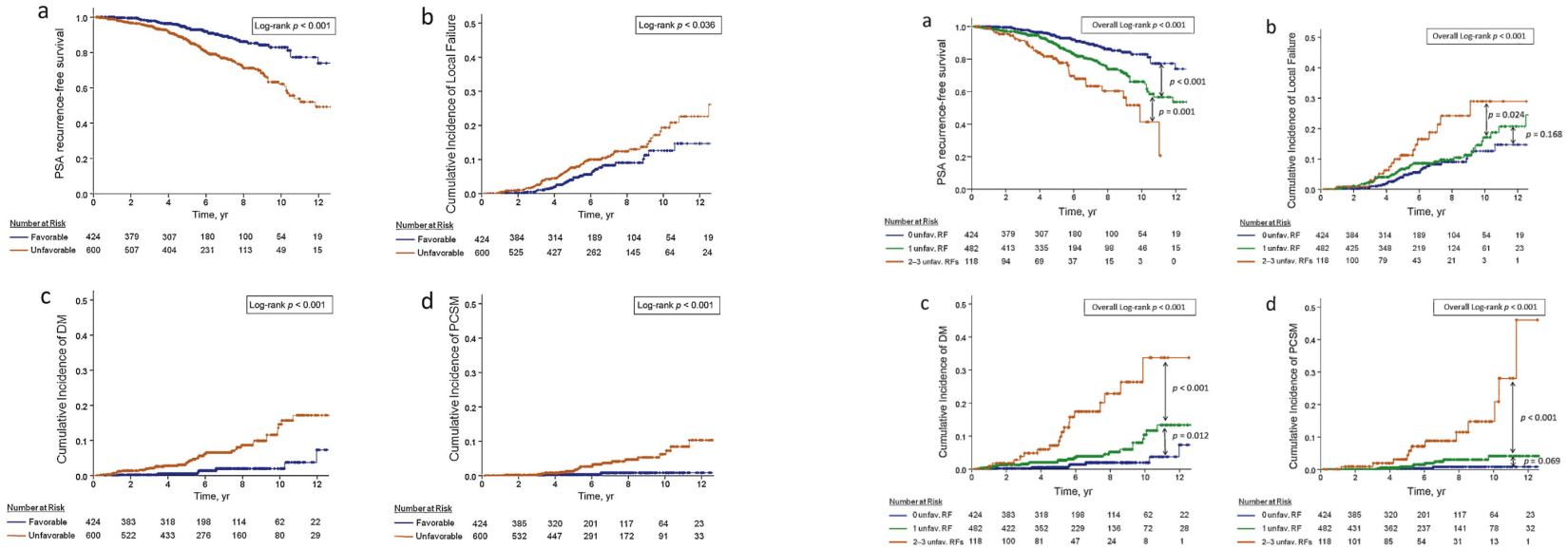
RADIOTHERAPY + ADT IN INTERMEDIATE RISK PC

Intermediate-risk PC is a **heterogeneous group of diseases**. In particular, *Zumsteg et al*. established the concept of:
favorable Intermediate risk vs unfavorable intermediate-risk disease

Memorial Sloan Kettering Reclassification[26]		
Clinical Characteristics	Favorable Intermediate-Risk[a]	Unfavorable Intermediate-Risk[b]
	1 intermediate-risk factor[c]	> 1 intermediate-risk factor
	GS 3+4=7 or less	GS 4+3=7
	< 50% positive biopsy cores	≥ 50% positive biopsy cores

Zumsteg, et al 2013

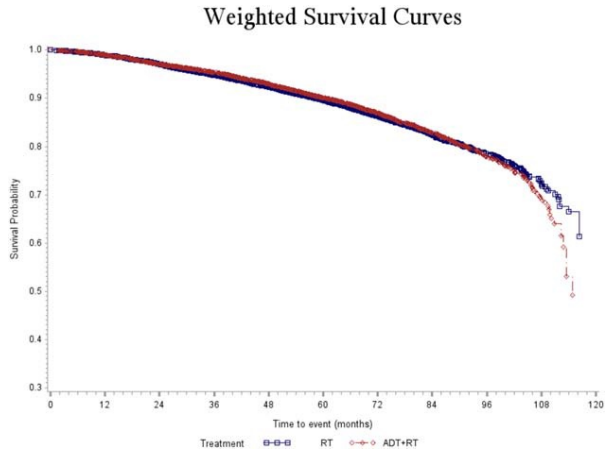
RADIOTHERAPY + ADT IN INTERMEDIATE RISK PC



"..IR PCa is a heterogeneous collection of diseases that can be separated into favorable and unfavorable subsets. These groups likely will benefit from divergent therapeutic paradigms.."

Zumsteg, et al 2013

RADIOTHERAPY + ADT IN FAVOURABLE INTERMEDIATE RISK PC



Original Article

Evaluation of the Effectiveness of Adding Androgen Deprivation to Modern Dose-Escalated Radiotherapy for Men With Favorable Intermediate-Risk Prostate Cancer

Aaron D. Falchook, MD[1]; Ramsankar Basak, PhD[1]; Jahan J. Mohiuddin, BS[1]; and Ronald C. Chen, MD MPH[1,2]

"…the addition of ADT to modern dose-escalated RT was not associated with improved overall survival for any patient subgroup based on age or comorbidity score…"

Falchook AD, et al 2016

RADIOTHERAPY + ADT IN HIGH/VERY HIGH RISK PC

EUROPEAN UROLOGY 83 (2023) 267–293

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

European Association of Urology

Prostate Cancer – Editor's Choice

Management of Patients with Advanced Prostate Cancer. Part I: Intermediate-/High-risk and Locally Advanced Disease, Biochemical Relapse, and Side Effects of Hormonal Treatment: Report of the Advanced Prostate Cancer Consensus Conference 2022

15. In the majority of patients with high-risk localised (STAMPEDE definition) prostate cancer (≥2 out of 3 criteria: cT3/T4, PSA ≥40, Gleason 8–10) and N0 M0 on next-generation imaging, what is your recommended systemic therapy in combination with local radiation therapy?	1. ADT alone for 2–3 yr	21 (22)
	2. ADT for 2–3 yr plus abiraterone for 2 yr	78 (80), consensus
	3. ADT for 2–3 yr plus docetaxel 6 cycles	1 (1)
16. In the majority of patients with very-high-risk localised prostate cancer (NCCN definition: at least one of the following: cT3b-cT4, primary Gleason pattern 5, 2 or 3 high-risk features, >4 cores of ISUP grade group 4 or 5) and N0 M0 on next-generation imaging, what is your recommended systemic therapy in combination with radiation therapy to the primary?	1. ADT alone for 2–3 yr	17 (17)
	2. ADT for 2–3 yr plus abiraterone for 2 yr	78 (80), consensus
	3. ADT for 2–3 yr plus docetaxel 6 cycles	5 (5)

RADIOTHERAPY + ADT IN HIGH/VERY HIGH RISK PC

Clinical Investigation

Duration of Androgen Deprivation in Locally Advanced Prostate Cancer: Long-Term Update of NRG Oncology RTOG 9202

"…LTAD and RT is superior to STAD and RT for the treatment of locally advanced nonmetastatic adenocarcinoma of the prostate and should be considered the standard of care.."

High-dose radiotherapy and risk-adapted androgen deprivation in localised prostate cancer (DART 01/05): 10-year results of a phase 3 randomised, controlled trial

Almudena Zapatero, Araceli Guerrero, Xavier Maldonado, Ana Álvarez, Carmen González San-Segundo, María Ángeles Cabeza Rodríguez, Josep María Solé, Agustí Pedro Olivé, Francesc Casas, Ana Boladeras, Carmen Martín de Vidales, María Luisa Vázquez de la Torre, Susana Vara, Juan Luis Sanz, Felipe A Calvo

"…the benefit was clinically relevant in high-risk patients. IR Pca patients treated with high-dose radiotherapy do not benefit from LTAD.."

Duration of Androgen Deprivation Therapy in High-risk Prostate Cancer: A Randomized Phase III Trial

Abdenour Nabid[a,], Nathalie Carrier[a], André-Guy Martin[b], Jean-Paul Bahary[c], Céline Lemaire[d], Sylvie Vass[e], Boris Bahoric[f], Robert Archambault[g], François Vincent[h], Redouane Bettahar[i], Marie Duclos[j], Marie-Pierre Garant[a], Luis Souhami[j]*

"..In localized HRPC, our results support that 36 mo is not superior to 18 mo of ADT. ADT combined with RT can potentially be reduced to 18 mo in selected men without compromising survival.."

≠ inferior!

Lawton C, et al 2017
Zapatero A, et al 2022
Nabid A, et al 2018

"…these data suggest patients receiving dose-escalated external beam radiotherapy should receive a minimum of 18 months of ADT (supported by high-level data)…"

SUMMARIZING

- LOW- RISK

ADT is not recommended in the treatment of low-risk LPCa (ESTRO – EAU)

- INTERMEDIATE- RISK

ESTRO and the EAU currently recommend to add short-term ADT (6 months) to RT in patients with intermediate risk LPCa, irrespective of the subgroup

→ Favorable → option no ADT

→ Unfavorable → 6m ADT

- HIGH-RISK/LOCALLY ADVANCED

Long-term ADT is recommended in combination to RT in the treatment of HR LPCa EAU-ESTRO-guidelines

AIRO2023

Radioterapia Oncologica:
l'evoluzione al servizio dei pazienti

IL CASO CLINICO

IL PAZIENTE

- 25/08/1948; sposato, no figli, vive con la moglie
- 174 cm, 94 kg (BMI 31)
- Licenza elementare, operaio edile in pensione, vita sedentaria
- Ex fumatore (20 sig/die per 40 anni), vino ai pasti
- LUTS di lieve entità (IPSS: 8), alvo regolare, DE lieve-moderata (IIEF-5: 16)
- No storia chirurgia maggiore
- Nel 2014 STEMI con pPCI. In FU cardiologico
- Comorbidità: artrite psoriasica, dislipidemia, ipertensione.
- Terapia domiciliare: metotrexate + tp steroidea, fibrati, statine, calcio antagonista, clopidogrel

IL PAZIENTE

•4/2022: riscontro occasionale di PSA totale 6.8 ng/ml

•ER (4/2022): prostata x2, aumento di consistenza a sx

•RM mp (13/05/2022): P5 20 mm mediale lobo sx con associata irregolarità di capsuala, P4 6 mm apice sx, infiltrazione VS sx

•Bio prostatiche (3/6/2022): 12 prelievi random + 3/3 aree target: 8/12 pos GS 4+3 e 4+4, prelievi fusion pos per GS 4+4 e 4+5

•PET Colina di stadiazione (20/07/2022): patologico uptake a carico di prostata e di 2 linfonodi iliaco-otturatori sx, non uptake nodali extraregionali od ossei

STADIO: cT3b N1 M0 iPSA 6.8 ng/ml GS 4+5