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AIRO Piemonte Valle d'Aosta

L'integrazione ormono-radioterapica nei tumori della prostata incide sulle tossicità?

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Terapia ormonale

Circa il 75% dei pz. con carcinoma della prostata risponde ad una terapia ormonale.

Huggins, nel 1941, dimostrò sperimentalmente la correlazione fra:

- Crescita tumorale e stimolazione con androgeni.
- Blocco dell'espansione tumorale mediante deprivazione androgenica o somministrazione di estrogeni.

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Hormonal Therapy in CA Prostate

- Medical castration:
  - LHRH agonist: leuprolide, goserelin
  - LHRH antagonist: abarelix
- Surgical castration: bilateral orchidectomy
- Antiandrogen monotherapy
- Maximum androgen blockade

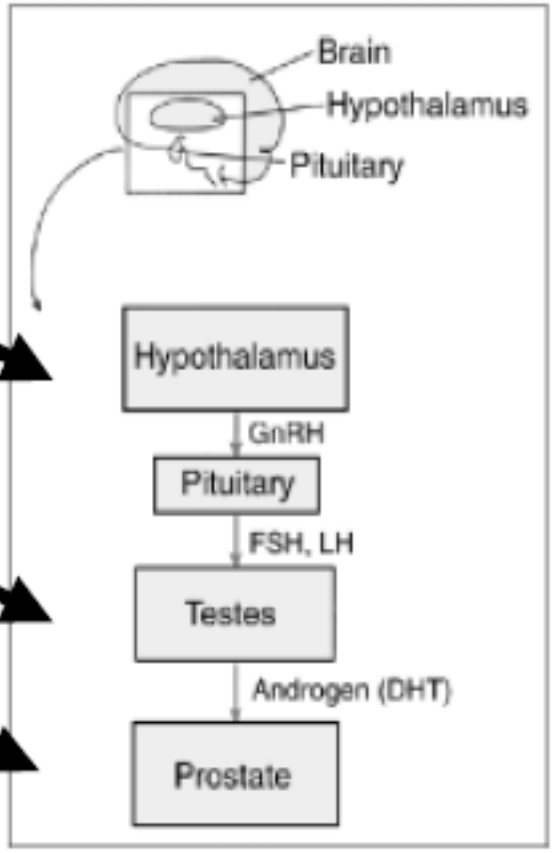

Figure 1. Interactions of hypothalamus, pituitary, and testes, and the production of the androgen, testosterone.

Terapia ormonale

La deprivazione androgenica determina:

- Rallentamento della crescita tumorale.
- Riduzione delle cellule tumorali per quiescienza e apoptosi.
- Raramente eradicazione completa della neoplasia.

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Modalità di associazioni ormonali con radioterapia

L'uso dell'endocrinoterapia in associazione alla radioterapia è stato studiato in 2 contesti:

- **Adiuvante** dopo radioterapia per pazienti ad alto rischio di metastasi occulte.
- **Neoadiuvante e concomitante** a scopo citoriduttivo in pazienti con tumori bulky o localmente avanzati al fine di potenziare il controllo locale.

Razionale del trattamento combinato nel carcinoma prostatico

- Citoriduzione
- Sinergismo d'azione sulla morte cellulare per via apoptotica
- Riduzione volumetrica con < ipossia e necrosi, < target radioterapico
- Blocco del ripopolamento cellulare accelerato

Zietman, 1997

Razionale del trattamento combinato nel carcinoma prostatico

- Miglior distribuzione di dose e risparmio dei tessuti sani dopo ormonoterapia neoadiuvante alla radioterapia grazie alla riduzione volumetrica della ghiandola.

  Zelefsky, 1997

- Dopo 3 mesi di terapia ormonale neoadiuvante prechirurgica volume prostatico da 41 a 25 cc.

  Gleave, 2001

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Radioterapia + ormonoterapia: studi clinici

Phase III studies using the combination of radiotherapy and androgen suppression

Study, author, year, reference	Patients	Study design	Conclusions	Comments
EORTC 22863 (Bolla et al., 2002) [20]	415 pts, high-risk : T3–4 (89%) or T1–2 WHO 3	RT vs. RT + CAAD (3 years)	LC, DFS, OS advantage with AD	Pelvis 50 Gy + 20 Gy prostate boost
RTOG 8531 (Pilepich et al., 2005) [160]	977 pts, high-risk: T3 (15%) or T1–2, N+ or pT3 and (+) margin or (+) SV	RT (AD at failure) vs. RT + AAD indefinite	LC, DFS, DM, OS advantage with AD for GS 8–10	Pelvis 44-46 Gy + prostate boost of 20–25 Gy (prostate bed only to 60–65 Gy in postop RT). Pre-PSA study
RTOG 8610 (Pilepich et al., 2001) [159]	456 pts, high-risk: bulky T2b, T3–4, N+ allowed	RT vs. RT + NCAD (4 months)	OS advantage with AD for GS <7	Pelvis 44–46 Gy + prostate boost of 20–25 Gy. Pre-PSA study
RTOG 9202 (Hanks et al., 2003) [73]	1554 pts, high-risk: T2c–4, PSA < 150 ng/mL, N+ allowed	RT + NCAD (4 months) vs. RT + NCAD (4 months) + AAD (24 months)	DFS, OS advantage with 24 month AAD for GS 8–10	Pelvis 4–46 Gy + prostate boost of 20–25 Gy
RTOG 9413 (Roach et al., 2003) [173]	1323 pts, intermediate to high-risk: T2c–4 GS ⩾6 or risk of N+ >15%, PSA < 100 ng/mL	WP + NCAD (4 months) vs. WP + AAD (4 months) vs. PO + NCAD (4 months) vs. PO + AAD (4 months)	PFS advantage with NCAD + WP	2 × 2 factorial design to study the impact of AD timing and RT field size

Radioterapia + ormonoterapia: studi clinici

- NHT vantaggiosa in pz. a rischio intermedio
- NHT senza “long term“ AHT inadeguata in pz. ad alto rischio
- Durata NHT: >2 mesi +2-4 mesi concomitante
- I pazienti ad alto rischio beneficiano di NHT e AHT (per almeno 2 anni)

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Radioterapia esterna: tossicità

Sintomi urinari irritativi /ostruttivi	Incont. urinaria	Disfunz. erettile	Proctite	Sanguin. rettale tardivo
Late ≥ G2: 10% (RTOG 9406, CRT)	1-2%	40-50% Sildenafil efficace	Late ≥ G2: 10% (RTOG 9406, CRT)	8-32% (tecnica e dose)

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Ormonoterapia: tossicità

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Riduzione della potenza sessuale e della libido

Astenia - Anemia

Osteoporosi

Riduzione masse muscolari

Sindrome metabolica

Vampate-sudorazione

Depressione

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Risk of Fracture after Androgen Deprivation for Prostate Cancer

Yahaira B. Shahinian, M.D., Yong-Fang Kuo, Ph.D., Jean L. Freeman, Ph.D., and James S. Goodwin, M.D.

Metabolic and cardiovascular effects of androgen deprivation therapy.

Hakimian P, Blute M Jr, Kashanian J, Chan S, Silver D, Shabsigh R.

Division of Urology, Maimonides Medical Center, Brooklyn, NY and Columbia University, New York, NY, USA.

Men with prostate cancer who undergo long-term ADT are at greater risk of developing dyslipidaemia, insulin resistance, hyperglycaemia and metabolic syndrome. These metabolic and physiological changes are a direct result of the induced severe hypogonadism and might predispose patients to a greater risk of cardiovascular morbidity and mortality

Ormonoterapia: tossicità

Bicalutamide vs castrazione

- Potenziali vantaggi:
  - Mantenimento della funzione erettile
  - Mantenimento dell'interesse sessuale
  - Mantenimento della qualità di vita
  - Minor astenia, anemia, osteoporosi, depressione, ipotrofia muscolare

- Potenziali svantaggi:
  - Ginecomastia e mastodinia

Iversen et al, 2000

Radioterapia + ormonoterapia: tossicità – NHT

- Induce riduzione del volume target e della % di retto e vescica irradiati.

  Zelefsky et al, Urology,1997; Dearnaley et al, Clin Oncol, 2000

- If such shrinkage is not taken into account at the moment of radiotherapy treatment planning an increased risk of complications is possible.

  Schultheiss et al., IJROBP, 1997

Radioterapia + ormonoterapia: tossicità – NHT

- La riduzione si protrae, più intensa, nei primi 3 mesi, per un periodo variabile tra 6 e 9 mesi.

  Sanguineti et al, Radiother Oncol, 2003

- Un inizio troppo precoce della RT (<2 mesi) si associa ad aumento della tossicità tardiva GU e GI.

  Liu et al, IJROBP, 2004

- AD does not seem to decrease delayed proctopaty: the higher haemoglobin initial level is associated with a reduced level of rectal side effect. Reductions in haemoglobin level during 6 months androgen deprivation is sufficient to remove the protective effect of reductions in target volume.
- *Christie D et al, Radiother Oncol, 2005*

Radioterapia + ormonoterapia: tossicità – NHT

- VARIABILE PREDITTIVA SFAVOREVOLE PER TOSSICITA' GU ACUTA >=2

  Roach et al, JCO, 2003

- VARIABILE PREDITTIVA SFAVOREVOLE PER TOSSICITA' GI TARDIVA >=2

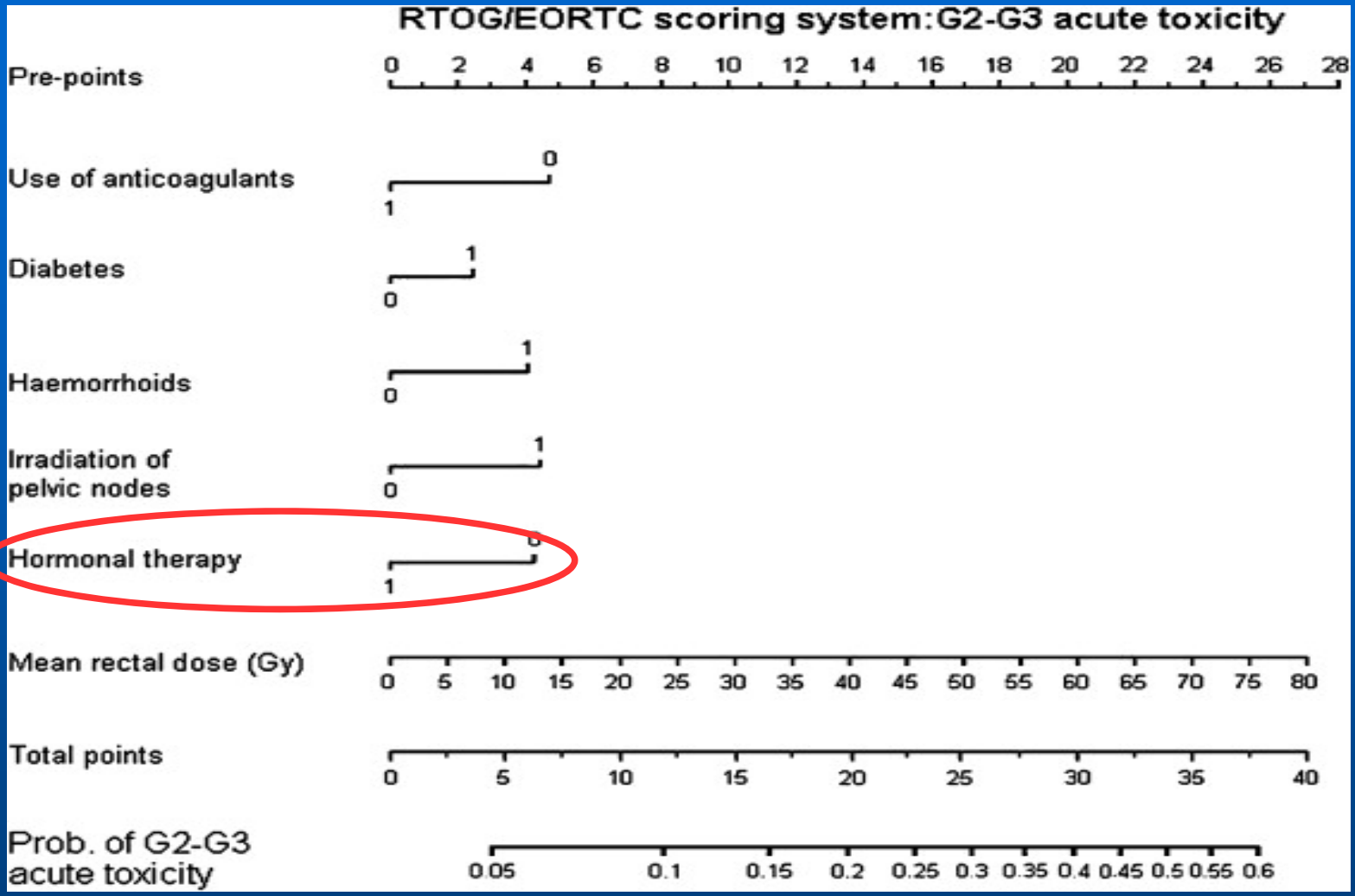
  Hanks et al, JCO, 2003

  Schulteiss et al, IJROBP,1997

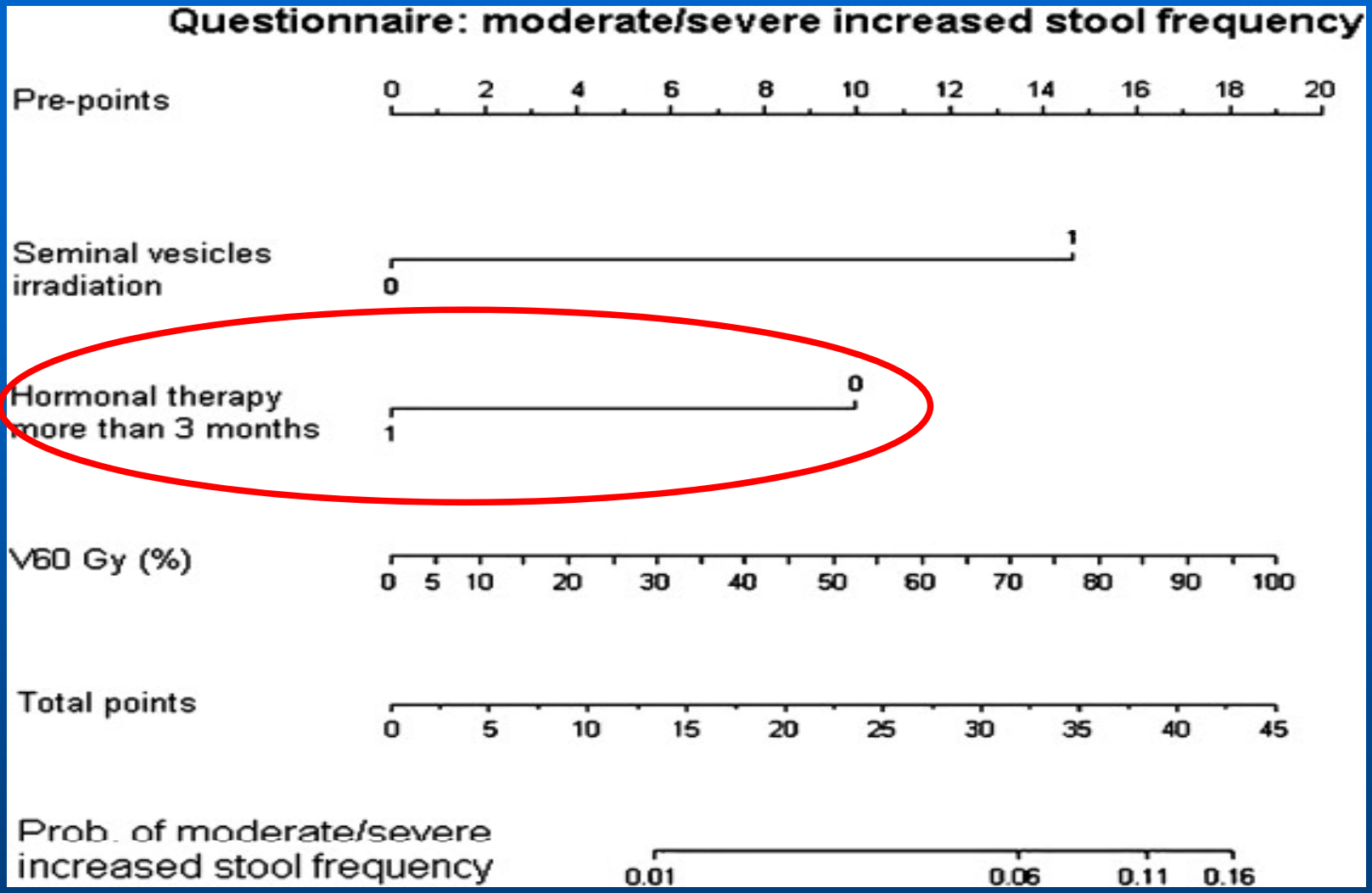
- VARIABILE PREDITTIVA FAVOREVOLE PER TOSSICITA' GI ACUTA >= 2

  Peeters et al, IJROBP, 2005

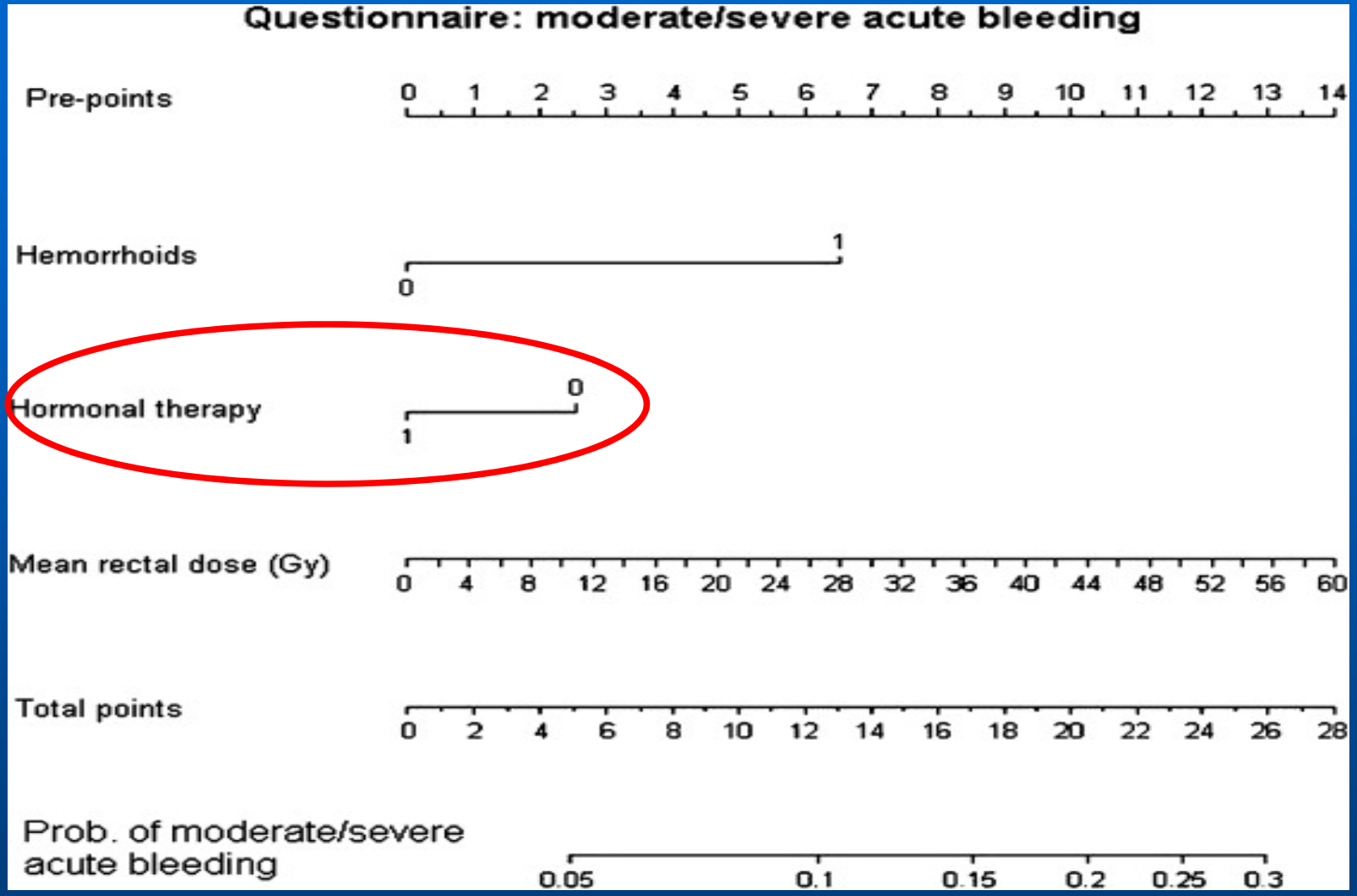
  Valdagni et al. AIRO PROS 01-02, IJROBP 2008



Nomogram for moderate/severe RTOG-EORTC lower gastrointestinal acute toxicity
Valdagni et al. AIRO PROS 01-02, IJROBP 2008



Nomogram for moderate/severe acute increased bowel frequency
Valdagni et al. AIRO PROS 01-02, IJROBP 2008



Nomogram for moderate/severe acute bleeding
Valdagni et al. AIRO PROS 01-02, IJROBP 2008

Radioterapia + ormonoterapia: tossicità – AHT

- VARIABILE PREDITTIVA SFAVOREVOLE PER TOSSICITA' GU TARDIVA >=2

  Bolla et al, Lancet, 2002

  Feigenberg et al, IJROBP, 2005

- VARIABILE PREDITTIVA SFAVOREVOLE PER TOSSICITA' GI TARDIVA >=2

  Hanks et al, JCO, 2003

  Feigenberg et al, IJROBP, 2005

  Sanguineti et al, BJC, 2002;

  Fiorino et al, Radiother Oncol, 2002

Radioterapia + ormonoterapia: tossicità

- A biological mechanism for the association of AD with GI and GU toxicity cannot be ruled out. A common mechanism such a vascular mediated effect could be hypothesized.

  Schultheiss et al, IJROBP, 1997

- The duration of HT before RT is now an important consideration and may influence side effect and tumor control.

  Valicenti R, IJROBP, 2003 (RTOG 94-06)

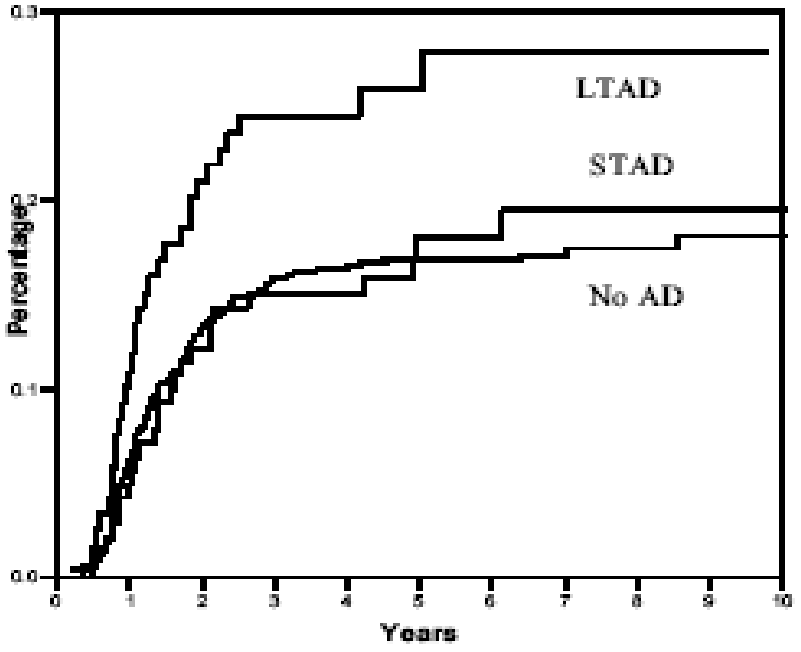
- The adjuvant androgen deprivation slows the riparative process of the irradiated rectum, increasing the susceptibility to developing a late rectal injury.

  Sanguineti et al, BJC, 2002; Feigenberg et al, IJROBP, 2005

Table 1. Patient and treatment characteristics

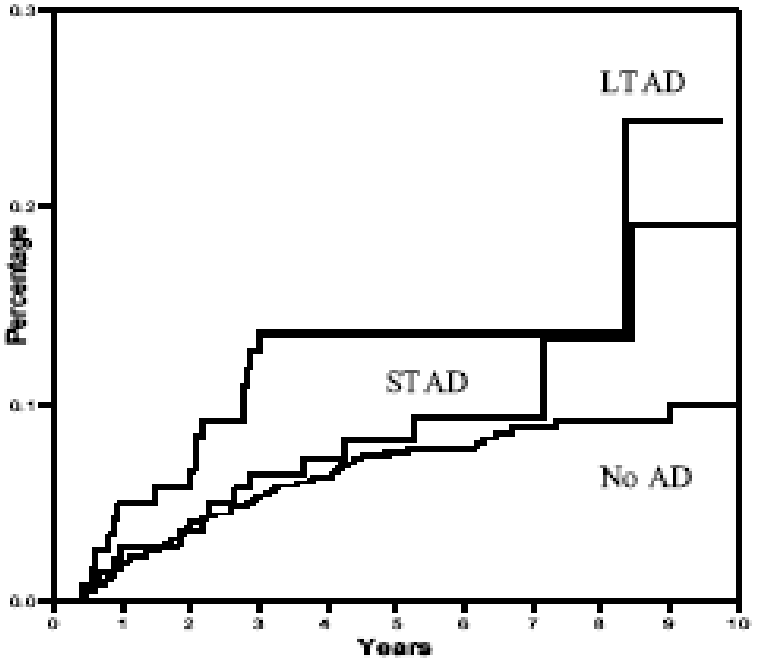
Characteristic	No AD (n = 945)	STAD (n = 140)	LTAD (n = 119)
Age (y)	69 (45–89)	69 (45–89)	68 (52–82)
Follow-up (mo)	66 (24–157)	74 (24–126)	55 (25–115)
PSA (ng/mL)			
< 10	553 (58.5)	44 (31.4)	24 (20.2)
10 to 20	269 (28.5)	46 (32.9)	40 (33.6)
> 20	123 (13.0)	50 (35.7)	55 (46.2)
Gleason Score			
2–6	708 (74.9)	74 (52.9)	31 (26.1)
7	197 (20.8)	51 (26.4)	43 (36.1)
8–10	40 (4.2)	15 (10.7)	45 (37.8)
T stage			
T1/T2a	571 (60.4)	33 (23.6)	24 (20.2)
T2b/T3	374 (39.6)	107 (76.4)	95 (79.8)
Diabetes (yes)	128 (13.5)	17 (12.1)	12 (10.1)
Total dose (Gy)	75 (63–84)	77 (64–82)	78 (61–82)
Fields			
Prostate alone	479 (50.7)	13 (9.3)	3 (2.5)
Partial pelvis	111 (11.7)	7 (5.0)	6 (5.0)
Whole pelvis	355 (37.6)	120 (85.7)	110 (92.4)
Rectal shielding (yes)	283 (29.9)	62 (44.3)	76 (63.9)

Feigenberg et al, IJROBP, 2005



At risk	LTAD	106	94	85	61	37	0
At risk	STAD	133	123	116	95	77	1
At risk	No AD	887	820	759	605	466	37
Cumulative							
GI events	LTAD	13	25	29	29	30	31
GI events	STAD	7	17	21	21	24	25
GI events	No AD	58	125	140	154	156	159

Fig. 3. Androgen deprivation as a predictor of Grade 2 and higher gastrointestinal morbidity. Patients at risk for each AD group (and events incurred) per year are shown. LTAD = long-term androgen deprivation (>6 months); No AD = no androgen deprivation; STAD = short-term androgen deprivation (≤6 months).



At risk	LTAD	113	112	96	73	45	0
At risk	STAD	136	135	120	105	88	1
At risk	No AD	927	907	813	683	535	47
Cumulative							
GU events	LTAD	6	7	16	16	16	17
GU events	STAD	4	5	9	10	11	15
GU events	No AD	18	38	51	58	67	74

Fig. 5. Androgen deprivation as a predictor of Grade 2 and higher genitourinary morbidity. Patients at risk for each AD group (and events incurred) per year are shown. LTAD = long-term androgen deprivation (>6 months); No AD = no androgen deprivation; STAD = short-term androgen deprivation (≤6 months).

Feigenberg et al, IJROBP, 2005

Radioterapia + ormonoterapia: tossicità

- Testosterone suppression in men with prostate cancer leads to an increase of arterial stiffness and hyperinsulinaemia.

  Dockery et al, Clin Sci, 2003; Smith et al, J Clin End.Met, 2001; Keating et al, JCO, 2006

- Late toxicity might be enhanced because recovery of radiation injury in surrounding normal tissues could be delayed by AHT.

  Ishikawa et al, IJROBP, 2008

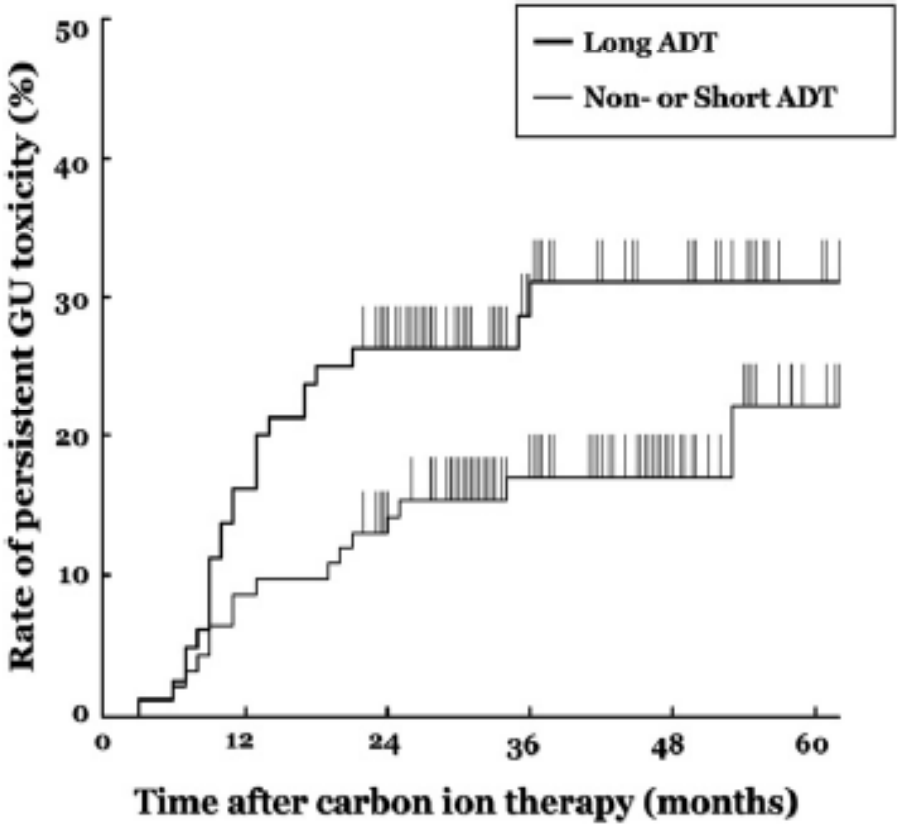


Fig. 2. Cumulative Grade 1-2 persistent genitourinary complication rates according to use of long-course (≥24 months) androgen deprivation therapy (ADT). Five-year complication rate for patients treated with long-course ADT was 31.1% compared with 22.2% for those treated with short-course ADT or no ADT ($p = 0.04$).

Table 4. Multivariate analysis for risk factors of Grade 1-2 morbidity

Characteristic	Hazard ratio	95% CI	*p*
Age	1.74	0.90–1.74	0.101
Long-course ADT	2.25	1.16–4.34	0.016
Acute toxicity	1.89	1.01–3.56	0.048
PTV	1.92	0.93–3.99	0.078
Length of urethra	1.33	0.64–2.80	0.447

Ishikawa et al, IJROBP,2008

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Radioterapia +ormonoterapia: tossicità Funzione sessuale

- We are not able to demonstrate that the addition of HT to 3D-CRT caused a greater change in SF than 3D-CRT alone.

  Chen CT et al, IJROBP, 2001

- Maximal androgen deprivation does not increase the probability of long term sexual dysfunction.

  Lamb DS et al, Radiother Oncol, 2003

- There are signicative diferences in gynecomastia and erectile disfunction between 3D-CRT + NHT vs 3D-CRT alone.

  D'Amico AV et al, JAMA, 2004

Radioterapia + ormonoterapia: tossicità
Funzione sessuale

- There was no difference in frequency or time of return of sexual potency in 3DCRT + NHT vs 3DCRT alone.

  Pilepich et al, Urology, 1995 (RTOG 86-10)

- Gonadotropins profile after NHT and RT remain high at 1 year after treatment, suggesting possible Leydig and Sertoli cell damage by scattered radiation to the testis or by direct effect of LHRHa.

  Murthy et al, BJU, 1997

- Dose > 75.6 Gy and NHT are independent factors associated with increased % impotence.

  Zelefsky M et al, Cancer, 1999

Radioterapia + ormonoterapia: tossicità Conclusioni

- NHT induce riduzione del target
- E' importante la durata e l'associazione temporale
- In caso di NHT la RT va iniziata dopo un adeguato periodo di tempo (>2-3 mesi)
- AHT > 6 mesi incrementa il rischio di tossicità
- Il danno indotto da HT+RT è correlato a fibrosi e insufficienza vascolare oltre che al rallentamento dei processi riparativi.

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