



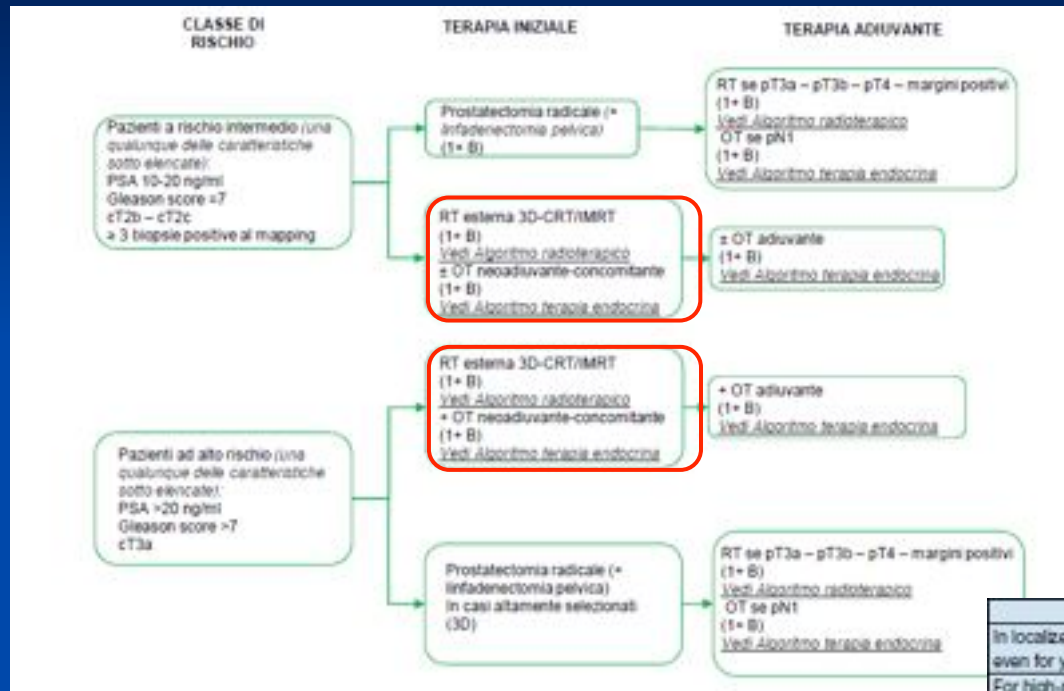
TOMO-RT moderatamente Ipofrazionata in pz con ADK Prostata a rischio intermedio/alto: outcomes clinici e tossicità in 85 pz trattati consecutivamente presso l' UO di RT di Modena.

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6-8 Novembre 2014

INTRODUZIONE -1



EAU GUIDELINES 2014

	LE	GR
In localized prostate cancer, T1c-T2c N0 M0, 3D-CRT with or without IMRT, is recommended, even for young patients who decline surgical intervention.	1b	B
For high-risk patients, long-term ADT before and during radiotherapy is recommended, as it results in increased overall survival.	2a	B
In patients with locally advanced PCa (T3-4 N0 M0), who are fit enough to receive EBRT, the recommended treatment is EBRT plus long-term ADT and the use of ADT alone is inappropriate.	1b	A
In patients with cT1-T2a, Gleason score < 7 (or 3 + 4), PSA ≤ 10 ng/mL, prostate volume ≤ 50 mL, without a previous TURP and with a good IPSS, transperineal interstitial brachytherapy with permanent implants can be an alternative.	2a	B
In patients with pathological tumour stage T3 N0 M0, immediate post-operative external irradiation after RP may improve the biochemical and clinical disease-free survival, with the highest impact in cases of positive margins.	1b	A
In patients with locally advanced PCa T3-4 N0 M0, concomitant and adjuvant hormonal therapy for a total duration of 3 years, with external-beam irradiation for patients with WHO 0-2 performance status, is recommended, as it improves the overall survival.	1b	A
In a subset of patients with T2c-T3 N0-X and a Gleason score of 2-6, short-term ADT before and during radiotherapy can be recommended, as it may favourably influence the overall survival.	1b	A
In patients with very high-risk PCa: c-pN1 M0, with no severe comorbidity, pelvic external irradiation and immediate long-term adjuvant hormonal treatment is recommended, as it may improve the overall survival, disease-specific failure rate, metastatic failure rate, and biochemical control.	2b	B

INTRODUZIONE -2

NCCN National Comprehensive Cancer Network® NCCN Guidelines Version 2.2014 Prostate Cancer

[NCCN Guidelines Index](#)
[Prostate Table of Contents](#)
[Discussion](#)

RISK GROUP	EXPECTED PATIENT SURVIVAL*	INITIAL THERAPY	ADJUVANT THERAPY
Intermediate: • T2b-T2c or • Gleason score 7 or • PSA 10-20 ng/mL	≥10 y [†]	RP [‡] + PLND if predicted probability of lymph node metastasis ≥2%	Adverse features: [‡] RT [§] or Observation [¶]
Very High: T3b-T4		RP [‡] + PLND (in select patients: with no fixation) or ADT [¶] in select patients ^{**}	Adverse features: [‡] RT [§] or Observation [¶] Lymph node metastasis: ADT [¶] (category 1) ± pelvic RT (category 2B) or Observation [¶] (category 2B)
Metastatic: Any T, N1		ADT [¶] or RT [§] + ADT [¶] (2-3 y) (category 1)	Adverse features: [‡] RT [§] or Observation [¶] Lymph node metastasis: ADT [¶] (category 1) ± pelvic RT (category 2B) or Observation [¶] (category 2B)
Any T, Any N, M1		ADT [¶]	Adverse features: [‡] RT [§] or Observation [¶]

PRINCIPLES OF RADIATION THERAPY
Primary External Beam Radiation Therapy (EBRT)
• Highly conformal RT techniques should be used to treat prostate cancer.
• Doses of 75.6 to 79.2 Gy in conventional fractions to the prostate (± seminal vesicles for part of the therapy) are appropriate for patients with low-risk cancers. For patients with intermediate- or high-risk disease, doses up to 81.0 Gy provide improved PSA-assessed disease control.
• Moderately hypofractionated and toxicity to conventionally fractionated IMRT regimens (2.4 to 4 Gy per fraction over 4-6 weeks) have been tested in randomized trials reporting similar efficacy and toxicity to conventionally fractionated regimens when clinically indicated.

ADJUVANT THERAPY
Undetectable PSA → [See Monitoring \(PROS-4\)](#)
Detectable PSA → [See Radical Prostatectomy, Hormonal Failure \(PROS-7\)](#)

NCCN 2014

*Patients with multiple adverse factors may be shifted to the next highest risk group.
†See Principles of Radiation Therapy (PROS-D).
‡See Principles of Surgery (PROS-3).
§Adverse laboratory/pathologic features include: positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA.
¶Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent. See Principles of Active Surveillance and Observation (PROS-C).
**See Principles of Androgen Deprivation Therapy (PROS-E).
***Primary therapy with ADT should be considered only for patients who are not candidates for definitive therapy.

INTRODUZIONE -3

Eur Urol. 2014 Aug 26. pii: S0302-2838(14)00751-9. doi: 10.1016/j.eururo.2014.08.009. [Epub ahead of print]

In press

A Systematic Review of Hypofractionation for Primary Management of Prostate Cancer.

Koontz BF¹, Bossi A², Cozzarini C³, Wiegel T⁴, D'Amico A⁵.



Biomed Res Int. 2014;2014:781340. doi: 10.1155/2014/781340. Epub 2014 Apr 30.

2014

BioMed Research International

Hypofractionation in prostate cancer: radiobiological basis and clinical appliance.

Mangoni M¹, Desideri I¹, Detti B¹, Bonomo P¹, Greto D¹, Paia F¹, Simontacchi G¹, Meattini I¹, Scoccianti S¹, Masoni T¹, Ciabatti C¹, Turkai A¹, Semi S², Minervini A², Gacci M², Carini M², Livi L¹.

J Clin Oncol. 2013 Nov 1;31(31):3860-8. doi: 10.1200/JCO.2013.51.1972. Epub 2013 Oct 7.

2013

Randomized trial of hypofractionated external-beam radiotherapy for prostate cancer.

Pollack A¹, Walker G, Horwitz EM, Price R, Feigenberg S, Konski AA, Stoyanova R, Movsas B, Greenberg RE, Uzzo RG, Ma C, Buyunouski MK.



...PROs and CONTRAs...

MATERIALI E METODI

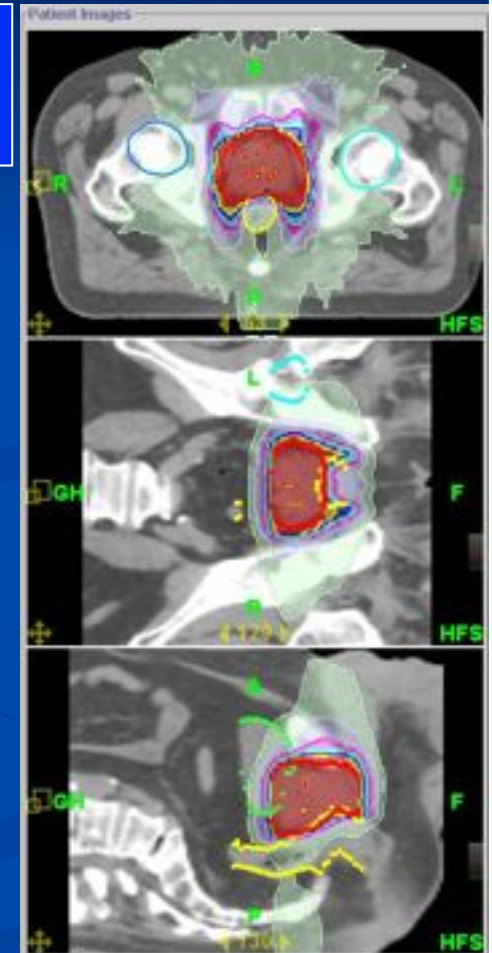


85 pz trattati consecutivamente con RT radicale
Luglio 2008 - Settembre 2013

Età Media 71.2 aa
Età Mediana 72 aa
KPS 90-100 → 91,8%

GS <6 in 23 pz
=7 in 33 pz
>7 in 29 pz

	T1	T2	T3a	T3b	T4	TOT
NO	11	34	16	18	0	79
N1	0	2	0	4	0	6
TOT	11	36	16	22	0	85



32/85 (37,6%) pz a rischio **intermedio** 53/85 (62,4%) pz a rischio **alto**

RISULTATI-1

- Durata trattamento RT: media $42,8 \pm 5,9$ SD giorni
- Dosi medie complessive:
 - PTV1: $70 \pm 2,6$ SD Gy (range 54-76 Gy)
 - PTV2: $62,2 \pm 5,2$ SD Gy (range 54-70 Gy)
 - PTV3: $51 \text{ Gy} \pm 1,7$ SD Gy (range 50,4-58,8)

2,2 – 3,82
Gy/Die

SIB 90%

Tutti i pazienti hanno completato il trattamento di RT + OT

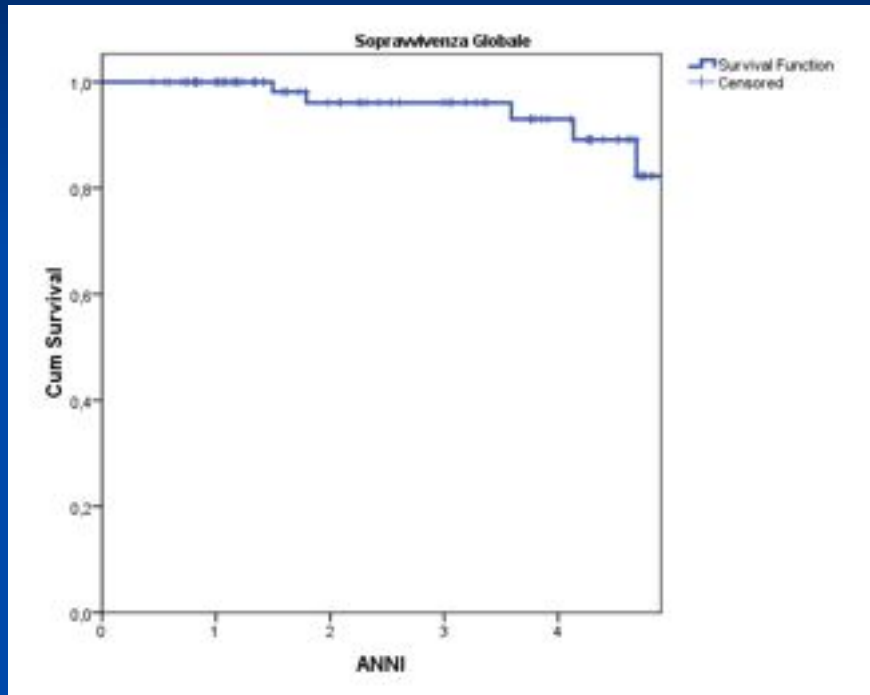


Sottoposti ad OT il 70,6% dei pazienti (60/85)

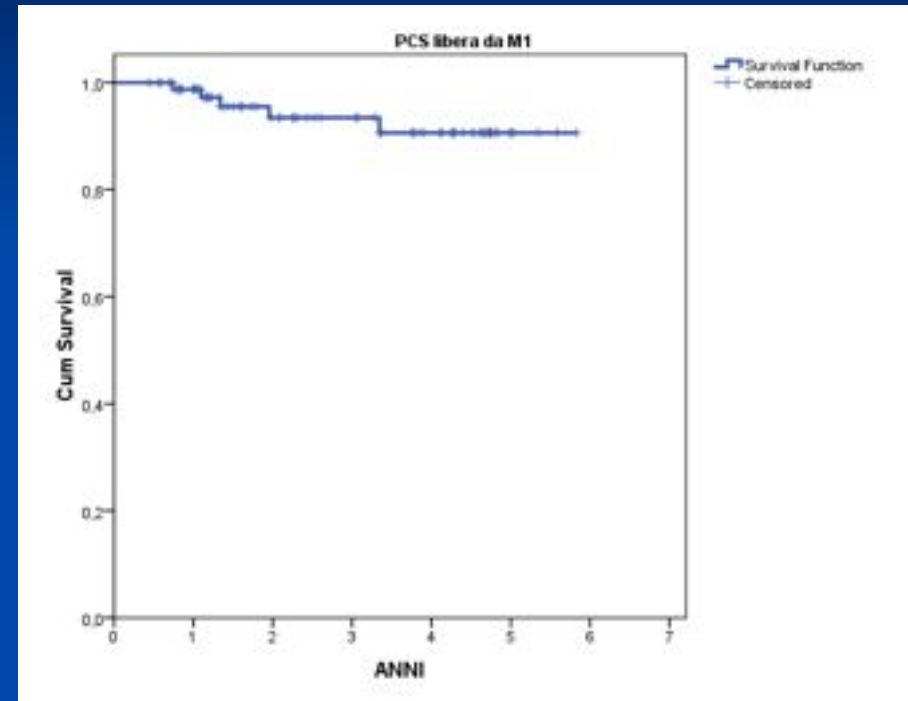
Follow-up mediano 27,7 mesi (range 5,4-70,9 mesi)

RISULTATI-2

Sopravvivenza Globale



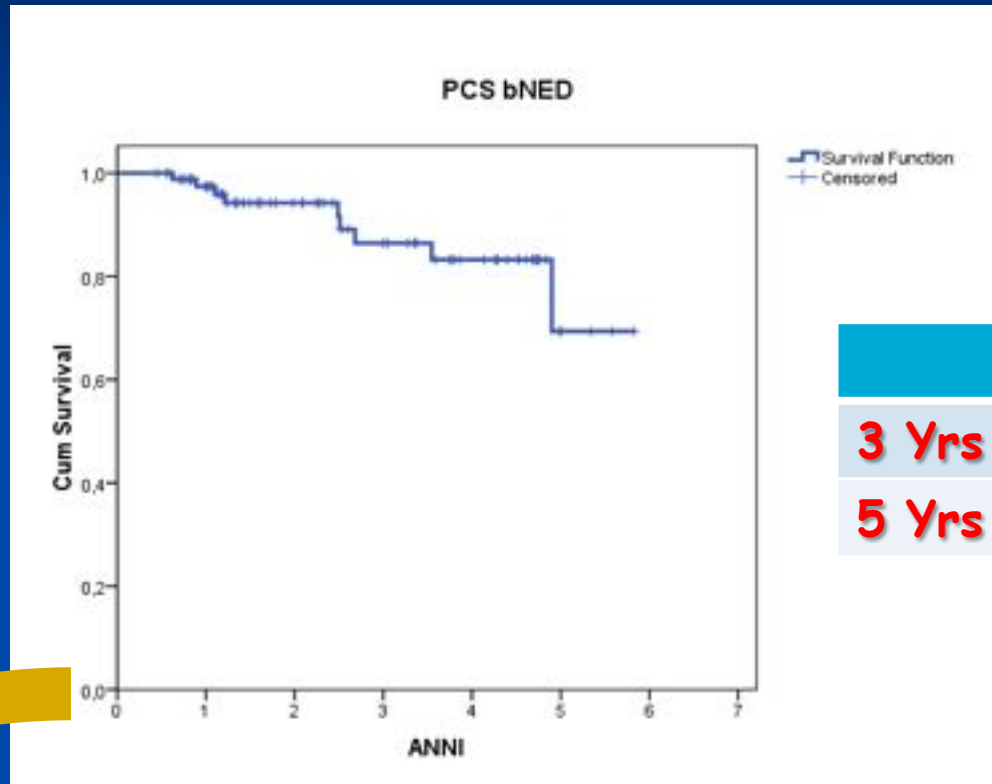
Sopravvivenza libera da MTS



	Overall Survival	Mts Free Survival
3 Yrs	96,0 +/- 2,7% ES	93,4 +/- 3,0%ES
5 Yrs	82,0 +/- 8,0% ES	90,6% +/- 4,0% ES

RISULTATI-3

Sopravvivenza libera da recidiva biochimica



	BF Survival
3 Yrs	86,4 +/- 5% ES
5 Yrs	70 +/- 13% ES



Analisi Univariata

Analisi Multivariata



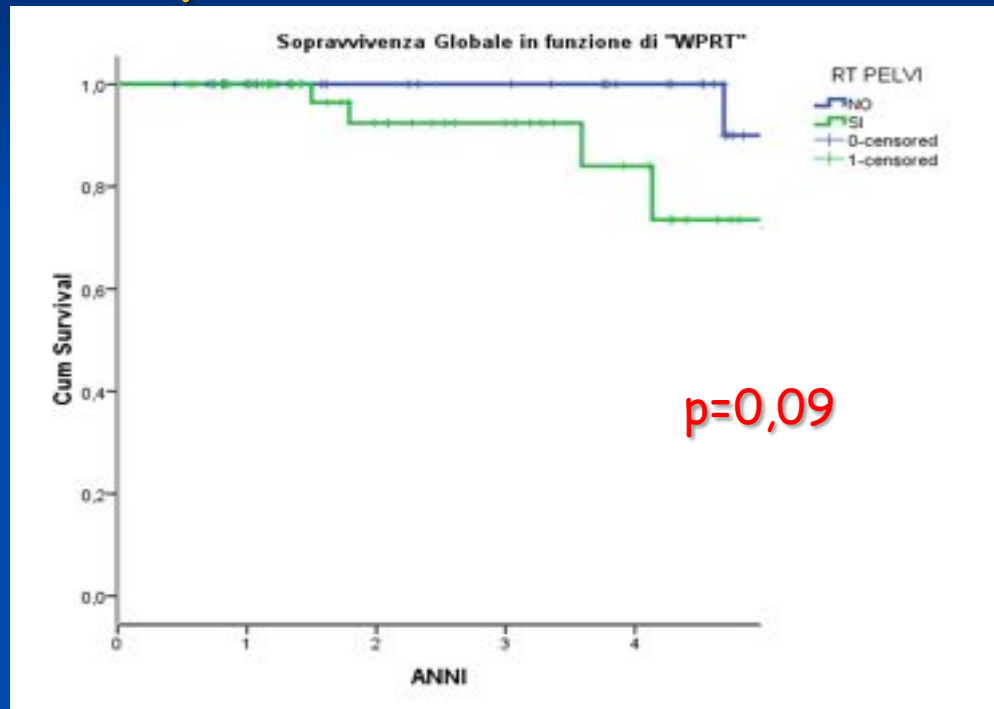
RISULTATI-4

Analisi Univariata

	OS	DMFS	bNED
Età	NS	NS	NS
KPS	NS	NS	NS
Gleason PS	NS	P <0,05	p= 0,04
T	NS	NS	NS
N	NS	P <0,008	P <0,01
iPSA	NS	NS	NS
Risk Class	NS	NS	p=0,06
Dose RT	NS	NS	NS
WPRT	p= 0,09	P <0,02	NS
OT	NS	NS	p= 0,01
PSA Nadir	NS	p=0,09	p= 0,02
Durata OT	NS	NS	NS

RISULTATI-5

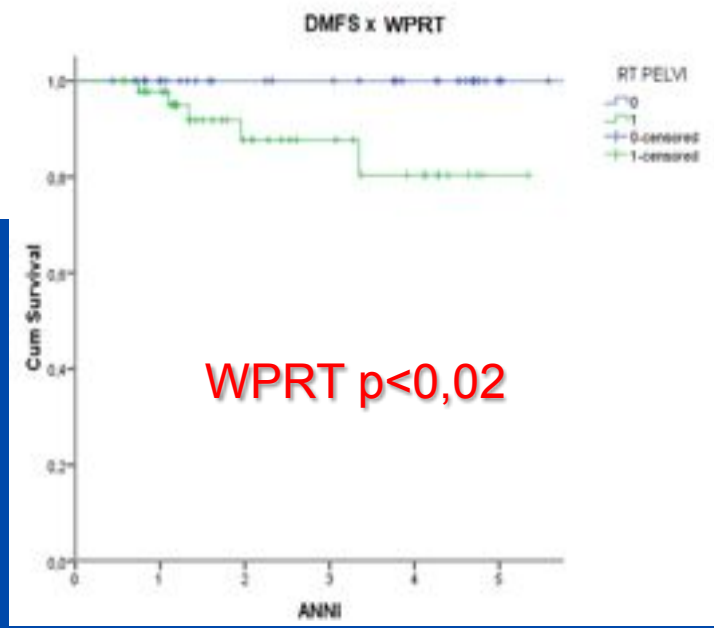
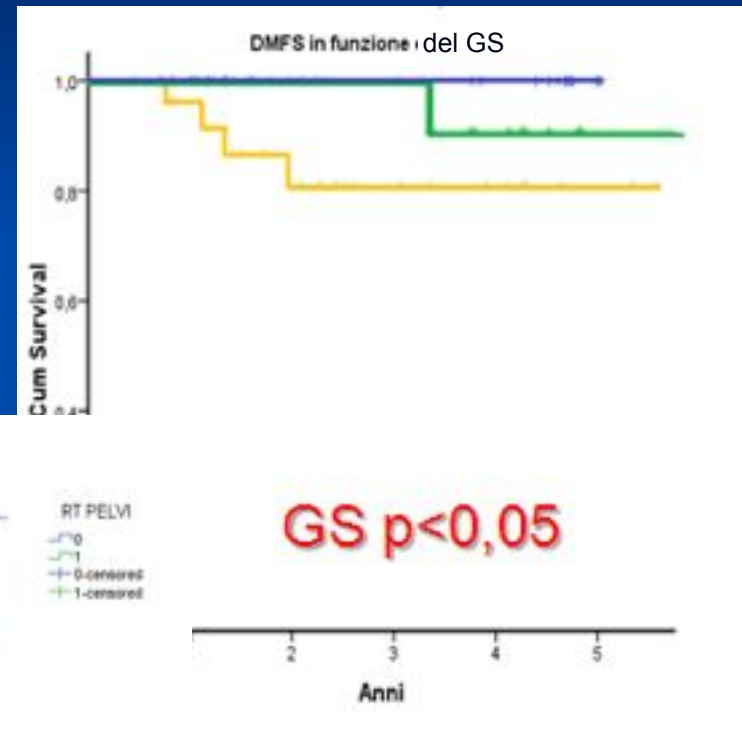
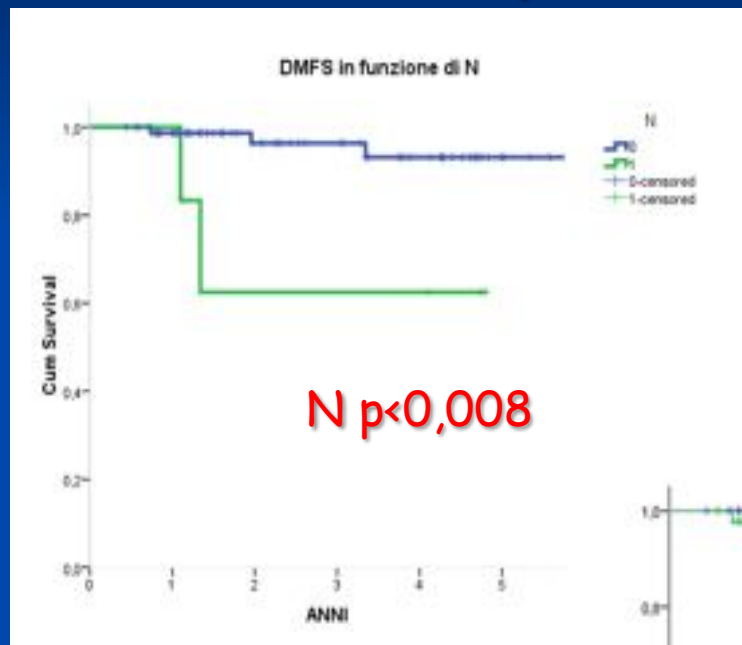
Analisi Univariata Sopravvivenza Globale



	3 YRS OS	5 YRS OS
NO WPRT	100% +/- 0,0 %ES	90 +/- 9,5%ES
YES WPRT	92,4 +/-5,2% ES	73,5% +/- 12,7% ES

RISULTATI-6

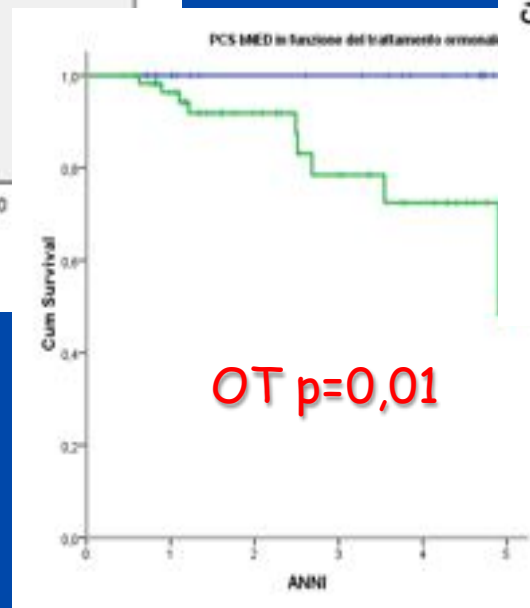
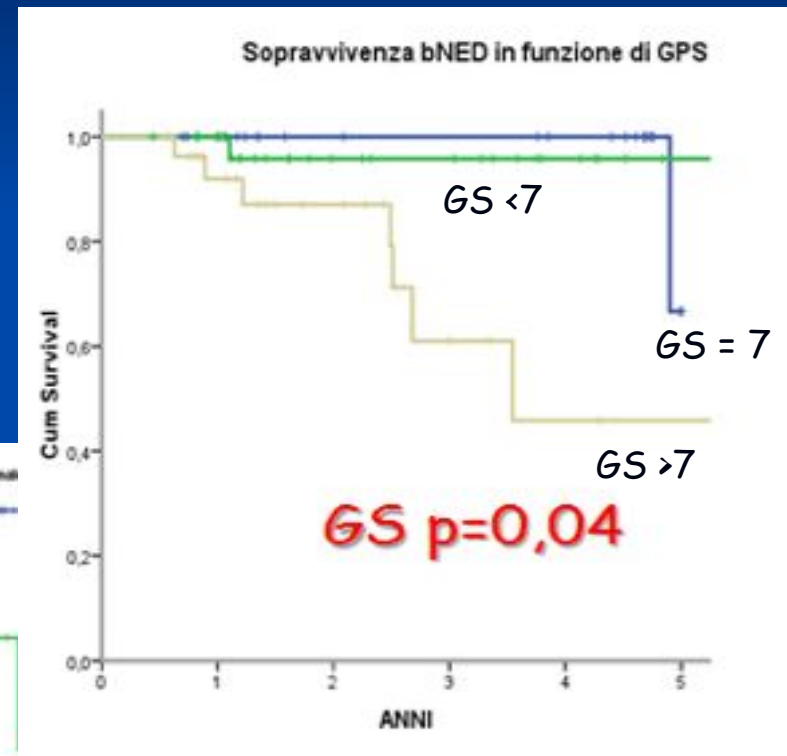
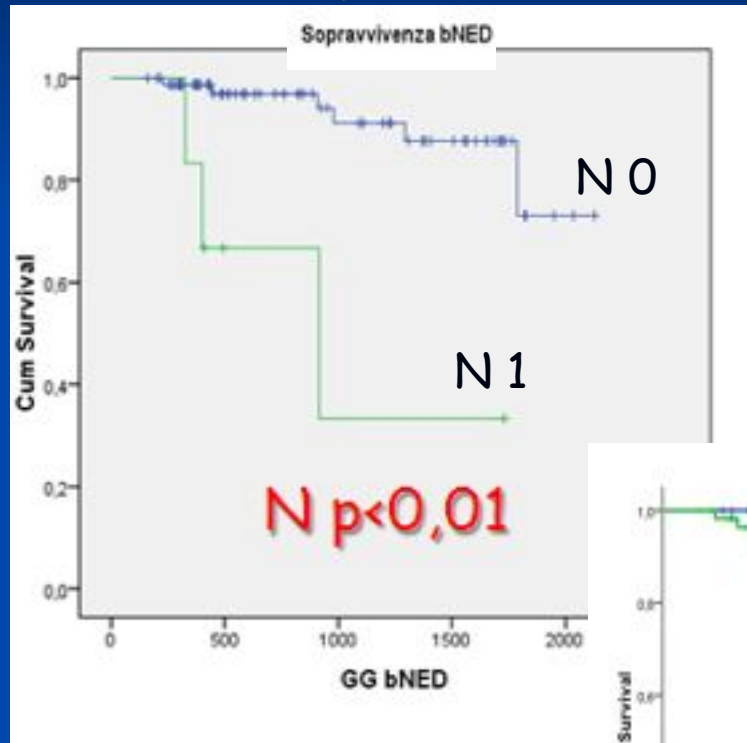
Analisi Univariata Sopravvivenza libera da metastasi



RISULTATI-7

Analisi Univariata

Sopravvivenza libera da recidiva biochimica



RISULTATI-8

Analisi Multivariata

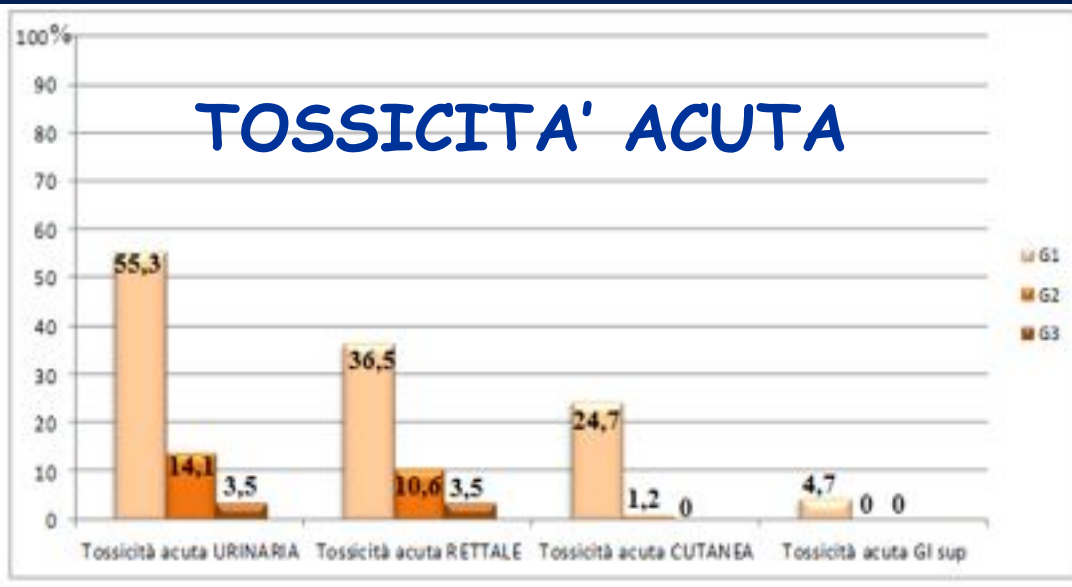
All'analisi multivariata nessun fattore prognostico è risultato statisticamente significativo per la sopravvivenza globale e libera da metastasi a distanza

MA...

	bNED
Gleason PS	p=0,005
Classe di rischio	p=0,09 (trend)
PSA Nadir	p=0,009

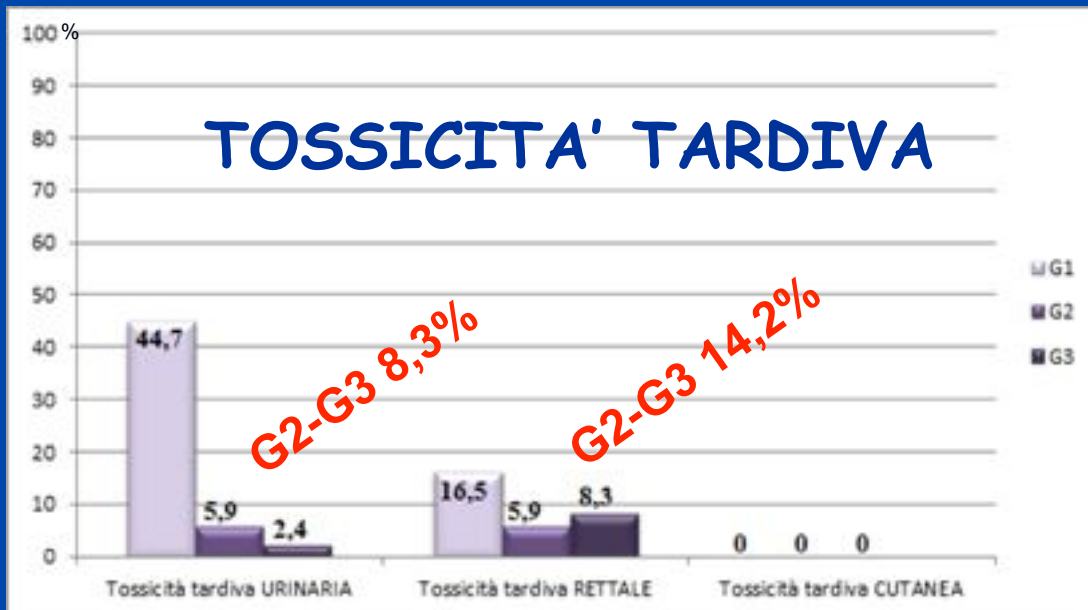
RISULTATI-9

TOSSICITA' ACUTA

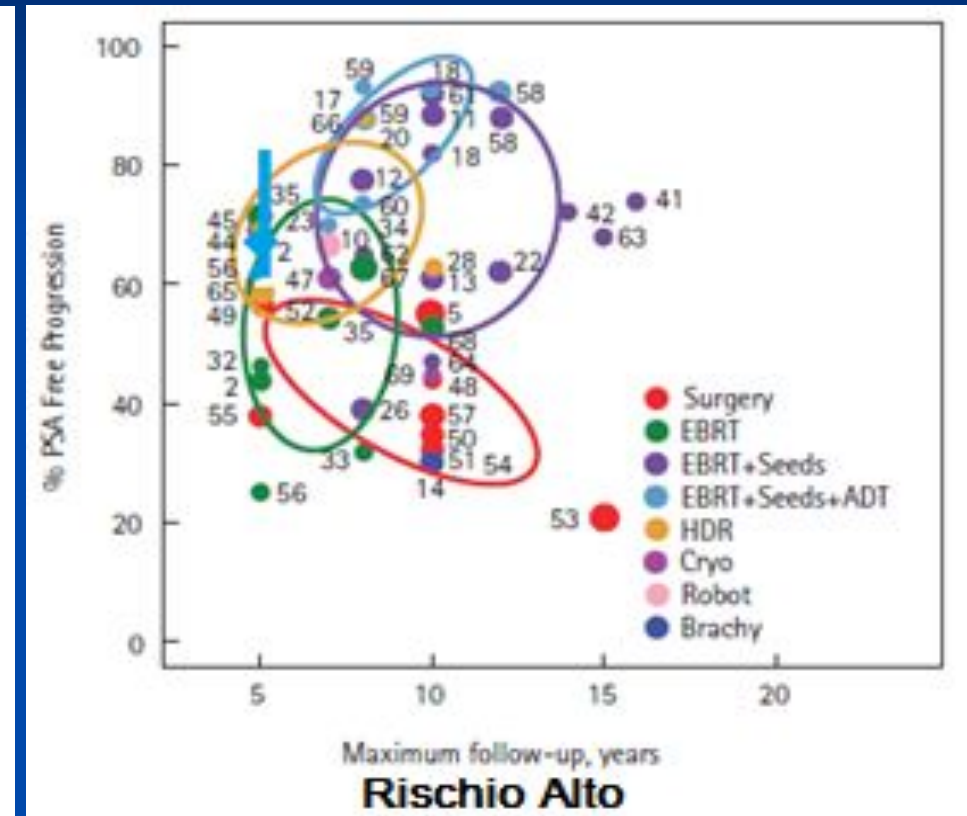
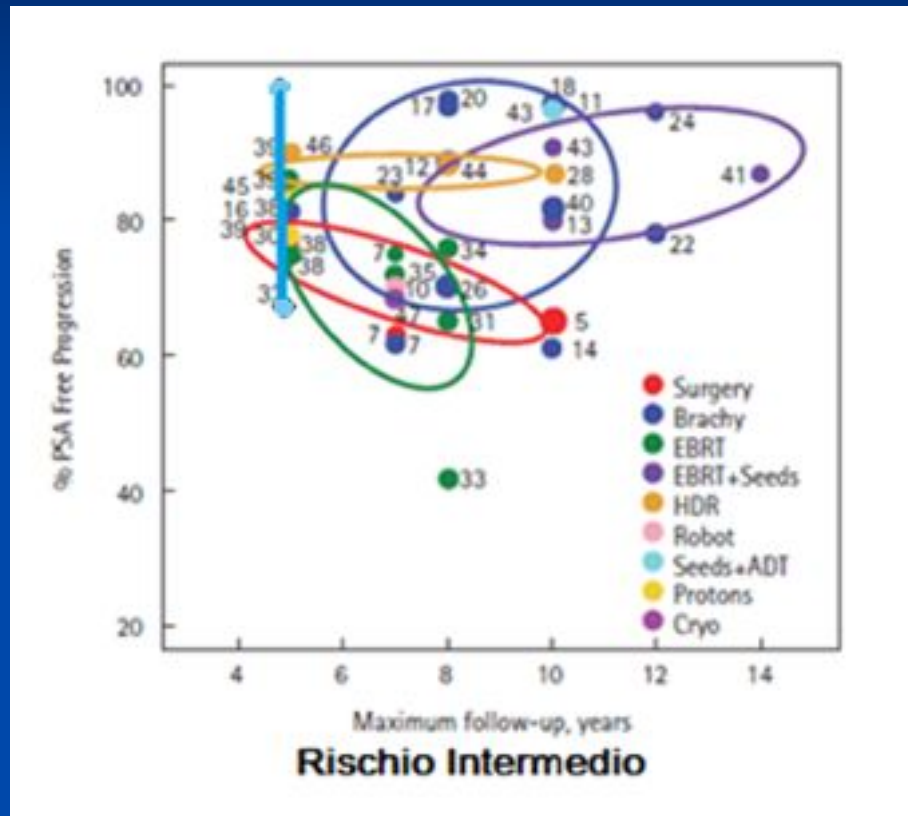


- 2 pz (2,4%) hanno dovuto sospendere temporaneamente il trattamento per tossicità acuta GI (1 pz per diarrea con febbre e leucocitosi, 1 pz per diarrea e rettorragia severa)
- 1 pz ha sospeso RT per 1 mese a causa di cistite batterica trattata con più linee antibiotiche non legata al trattamento radiante

TOSSICITA' TARDIVA



DISCUSSIONE-1



P. Grimm et al, BJUI, 2012

DISCUSSIONE -2

HFRT

Dose: 66 – 80 Gy Tox GI tardiva \geq G2 (%): **1,9 – 14**

Reference	n	Risk groups	Median FU (months)	Total dose (Gy)	Total fractions	Gy/fraction	BED (Gy), $\alpha/\beta =$		RTOG late toxicity Grade \geq 2 (%)	
Lukka ²¹	470	Low, intermediate, high	64	66	33	2	154	10	1.3	1.9
	466			52.5	20	2.63	144	66	1.3	1.9
Yeoh ^{22,23}	109	NR	90	64	32	2	149	77	NR	NR
	108			55	20	2.75	156	70	NR	NR
Arcangeli ²⁴⁻²⁶	85	High	35	80	40	2	187	96	16	17
	83			62	20	3.1	190	81	11	14
Pollack ^{27,28}	152	Intermediate, high	>60	76	38	2	177	91	8.3	5
	151			70.2	26	2.7	197	89	18.3	6.8
Kuban ²⁹	102	Mostly low, intermediate	56	75.6	42	1.80	166	89	19	6
	102			72	30	2.40	187	89	19	14

Zaorsky, N. et al. *Cancer Treat Rev*, 2013

CONCLUSIONI

Il trattamento moderatamente ipofrazionato con **IG-IMRT** mediante **Tomoterapia** si è dimostrato **efficace** con outcomes clinici soddisfacenti (5-aa OS=82,0%+/-8,0% ES)

Solo 2 pz hanno interrotto la RT (per 3-6 gg) dimostrando un' **ottimo profilo di tollerabilità** anche in trattamenti associati ad OT

Nessun fattore prognostico per DMFS e OS, tuttavia il **Gleason Pattern Score** ed il **PSA Nadir** sono risultati fattori prognostici indipendenti per **bNED**

Necessità di un **follow-up** più lungo per convalidare i risultati ottenuti oltre che di RCT di fase III.

PROSPETTIVE FUTURE

www.igimtrialunimore.it/index_prostata.php

IGIM Trial: Progetto di ricerca Regione-Università R.E.R.
"EFFICACIA E SICUREZZA CLINICA DELLA IGRT/IMRT IPOFRAZIONATA"
U.O. Radioterapia - Azienda Ospedaliero-Universitaria di Modena
Data center: Cattedra di Statistica - Università di Modena e Reggio Emilia

Accesso area riservata
Username:
Password:
Login

Protocollo di studio con ipofrazionamento più spinto con l'obiettivo di ottenere un miglioramento ulteriore del controllo locale senza un contestuale aumento della tossicità

**Arruolamento iniziato da circa 18 mesi
Arruolati 31 pz tra MO e BO**

Trattamento

- **Braccio convenzionale (braccio 1) 3D-CRT o IMRT:**
margine CTV-PTV non inferiore a 5 mm posteriormente e a 6 mm nelle altre direzioni
Basso rischio: il PTV deve ricevere 74 Gy in frazioni da 2 Gy
Rischio intermedio: il PTV deve ricevere una dose di 78 Gy in frazioni da 2 Gy
(Controllo convenzionale del posizionamento del centro).
- **Braccio sperimentale (braccio 2) IGRT/IMRT:**
margine CTV-PTV non superiore a 5 mm
Basso rischio: il PTV deve ricevere 54,30 Gy in 15 frazioni da 3,62 Gy prevedendo non più di 4 sedute di terapia a settimana.
Rischio intermedio: il PTV deve ricevere una dose di 57,30 Gy in 15 frazioni da 3,82 Gy prevedendo non più di 4 sedute di terapia a settimana.
(Verifica quotidiana on-line del posizionamento con IGRT volumetrica o con EPID nel caso siano stati impiantati nella prostata markers fiduciali).

Criteri d'inclusione

- Età > 18 anni
- Adenocarcinoma della prostata confermato istologicamente
- Stadio clinico T1b, T1c, T2a, T2b e T2c
- Gleason score ≤ 7
- PSA alla diagnosi ≤ 20 ng/ml Performance status < ECOG 2
- 5 anni (tranne tumori cutanei non

Criteri d'esclusione

- Precedente radioterapia a livello della pelvi
- Precedente prostatectomia
- Importanti patologie a carico del retto o del distretto genitourinario che controindichino la radioterapia
- Terapia ormonale che abbia avuto una durata superiore ai 2 mesi e interrotta meno di 2 mesi prima dell'inizio del trattamento.