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Italiana
Radioterapia
Oncologica

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WORKSHOP

Controversie nelle strategie terapeutiche del carcinoma prostatico localizzato ad alto rischio

Irradiazione pelvica: Pros - **P. Franzone** (Alessandria)

Irradiazione pelvica: Cons - **R. Santoni** (Roma)

XXI° CONGRESSO NAZIONALE AIRO

Genova, 19-22 novembre 2011

Magazzini del Cotone

Porto Antico

Prostate Cancer in comparison to Radiotherapy alone:

1 - RTOG 86-10 (2001)

456 patients with \geq



a-Goserelin 2 month before RT and during RT +
Cyproterone acetate (1 month)

vs

b-Pelvic irradiation (50 Gy) + Boost to the prostate (20 Gy)

3 - RTOG 92-02 (2008)

1554 patients with T2c - T4 and PSA < 150ng/ml

a-Goserelin + Flutamide 2 month before RT and during RT
(Short Antiandrogen Deprivation)

vs

b-Goserelin + Flutamide 2 month before RT and 24 additional
months (Long Antiandrogen Deprivation)

Randomized trials to test the use of Androgen Deprivation (AD) in Prostate Cancer in comparison to Radiotherapy alone:

RTOG 86-10

In GS 2 - 6 patients a short course of androgen ablation has been associated with a highly significant improvement of local control, reduction in disease progression and overall survival.

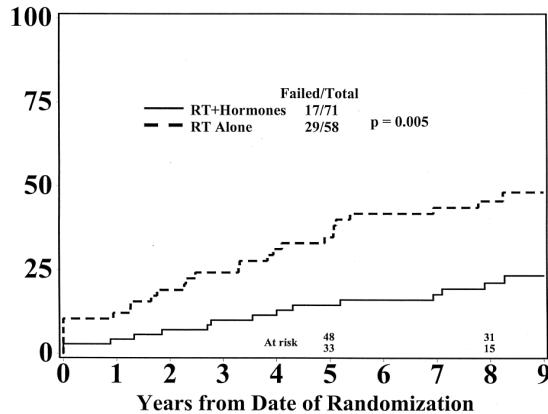


Fig. 6. Local progression, Gleason 2-6.

**Gleason 2 - 6:
Local progression**

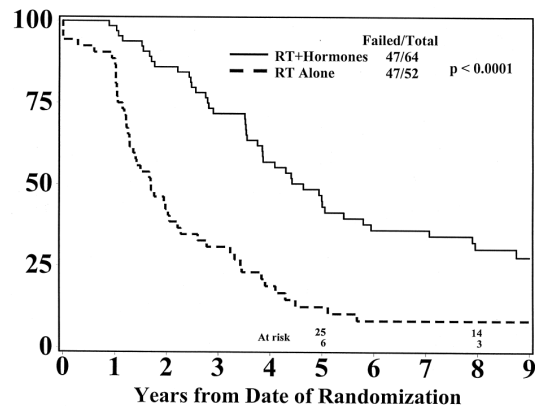


Fig. 7. bNED (PSA < 1.5), Gleason 2-6.

**Gleason 2 - 6:
bNED (PSA < 1.5)**

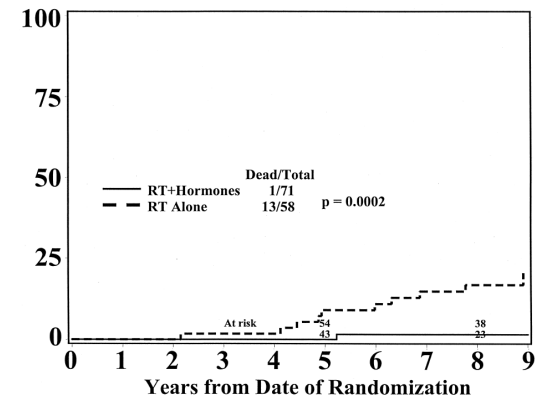


Fig. 8. Disease-specific mortality, Gleason 2-6.

**Gleason 2 - 6:
Disease spec. mortality**

Randomized trials to test the use of Androgen Deprivation (AD) in Prostate Cancer in comparison to Radiotherapy alone:

1 - RTOG 86-10 (2001)

456 patients with \geq T2 prostate cancer

a-Goserelin + Flutamide 2 month before RT and during RT

vs

b-Pelvic irradiation (45 Gy) + Boost to the prostate (20-25 Gy)

2 - EORTC Bolla M. and Genitourinary Group (2002)

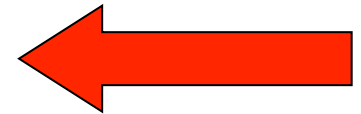
415 patients with T1 - 2 Grade III or T3 - 4

a-Goserelin 2 month before RT and during RT +

Cyproterone acetate (1 month)

vs

b-Pelvic irradiation (50 Gy) + Boost to the prostate (20 Gy)



3 - RTOG 92-02 (2008)

1554 patients with T2c - T4 and PSA < 150ng/ml

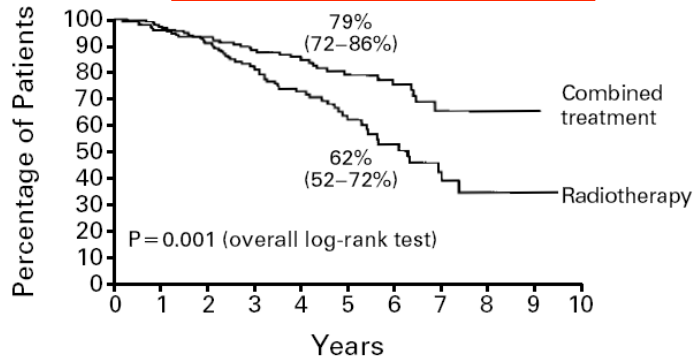
a-Goserelin + Flutamide 2 month before RT and during RT
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vs

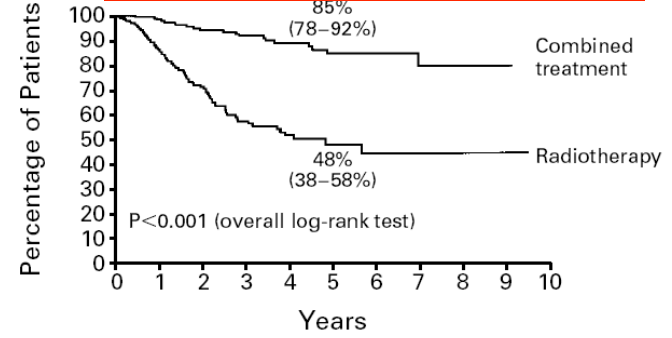
b-Goserelin + Flutamide 2 month before RT and 24 additional months (Long Antiandrogen Deprivation)

Bolla et al. EORTC Radiotherapy Cooperative Group

**Overall Survival:
79% vs 62%**



**Disease free interval:
85% vs 48%**



	No. OF PATIENTS AT RISK										No. WHO DIED
Radiotherapy	208	183	139	96	67	39	23	10	6	1	58
Combined treatment	207	190	144	111	82	55	39	19	7	0	35

	No. OF PATIENTS AT RISK										No. WITH DISEASE PROGRESSION
Radiotherapy	208	163	107	59	38	19	11	5	3	1	78
Combined treatment	207	189	138	108	78	51	36	16	5	0	20

TABLE 4. SITES OF DISEASE PROGRESSION.

TYPE OF PROGRESSION	RADIO-THERAPY	COMBINED TREATMENT
	no. of patients	
Any clinical progression	78	20
Local progression	8	3
Locoregional progression	5	0
Distant metastases	48	15
Distant and local metastases	15	2
Distant and locoregional metastases	2	0

T2 prostate cancer
a-Goserelin + Flutamide 2 month before RT and during RT

Cyproterone acetate (1 month) (2002)

vs

b-Pelvic irradiation (50 Gy) + Boost to the prostate (20 Gy)
Cyproterone acetate (1 month)

3 -

vs

~~RTOG 97-02 (2008)~~ b-Pelvic irradiation (50 Gy) + Boost to the prostate (20 Gy)
1554 patients with T2c - T4 and PSA < 150ng/ml

3 - ~~RTOG 97-02 (2008)~~ a-Goserelin + Flutamide 2 month before RT and during RT

1554 patients with T2c - T4 and PSA < 150ng/ml

b-Goserelin + Flutamide 2 month before RT and 24 additional months (Short Antiandrogen Deprivation)

vs

b-Goserelin + Flutamide 2 month before RT and 24 additional months (Long Antiandrogen Deprivation)



Ten-Year Follow-Up of Radiation Therapy Oncology Group Protocol 92-02: A Phase III Trial of the Duration of Elective Androgen Deprivation in Locally Advanced Prostate Cancer

Table 1. Pretreatment Characteristics for All Eligible Patients

Characteristic	STAD + RT (n = 763)		LTAD + RT (n = 758)		χ^2 Test P
	No.	%	No.	%	
Goserelin: 2 months, Flutamide Goserelin: 2 months, Flutamide					
Flutamide + Goserelin 24 months Flutamide + Goserelin 24 months					

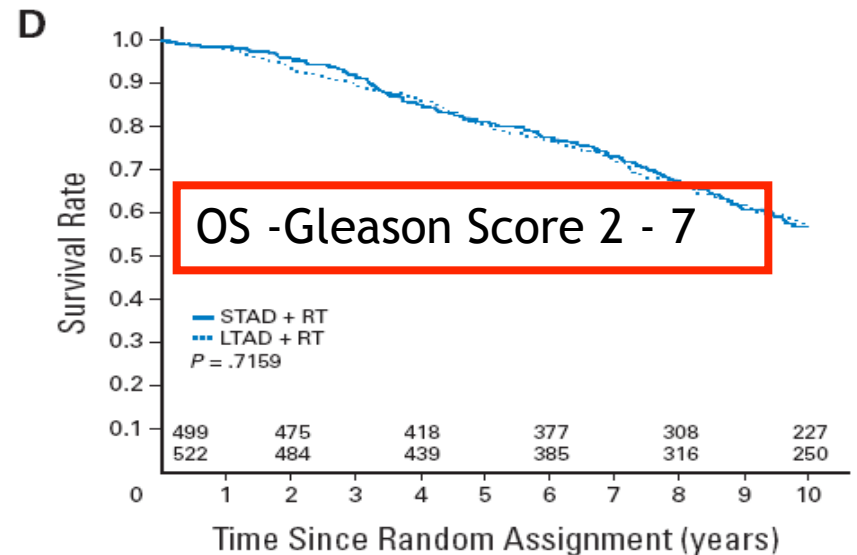
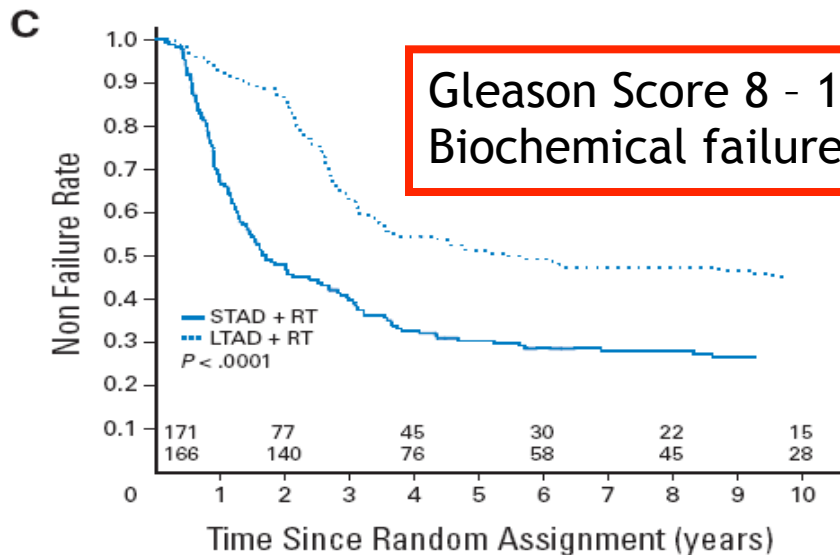
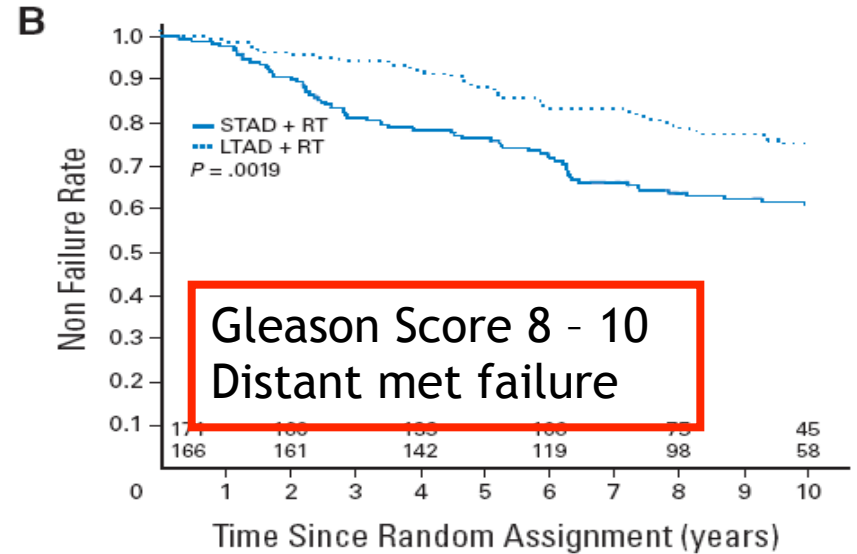
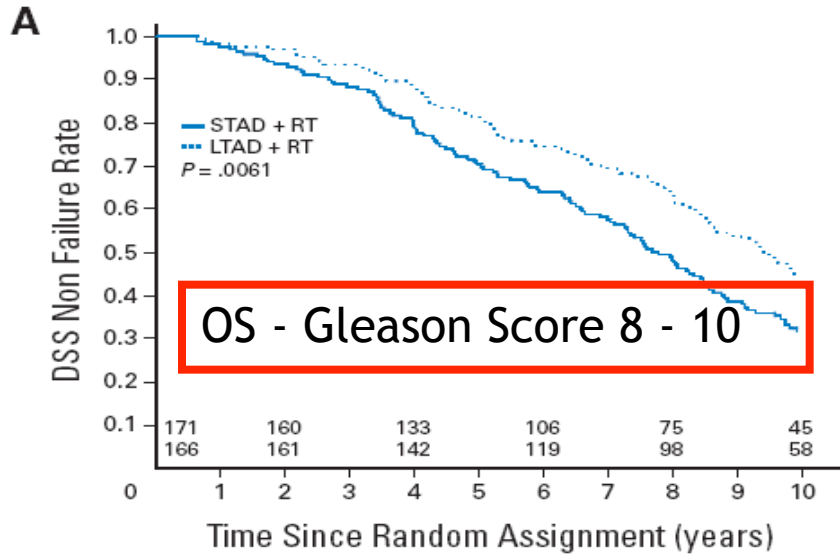
Table 3. 10-Year Treatment Outcomes for All Eligible Patients

Outcome	STAD + RT (n = 763)			LTAD + RT (n = 758)			Log-Rank χ^2 Test P
	No. of Failures	Estimated Rate	95% CI	No. of Failures	Estimated Rate	95% CI	
Disease-free survival	653	13.2	11 to 16	571	22.5	19 to 26	< .0001*
Overall survival	351	51.6	48 to 55	330	53.9	50 to 58	.3590
Disease-specific survival	116	83.9	81 to 87	80	88.7	86 to 91	.0042*
Local progression	166	22.2	19 to 25	90	12.3	10 to 15	< .0001*
Distant metastasis	167	22.8	20 to 26	107	14.8	12 to 17	< .0001*
Biochemical failure	513	68.1	65 to 71	384	51.9	48 to 55	< .0001*

Abbreviations: STAD + RT, short-term androgen deprivation with external-beam radiation therapy; LTAD + RT, long-term androgen deprivation with external-beam radiation therapy followed by goserelin.

*Statistically significant at .05.

Ten-Year Follow-Up of Radiation Therapy Oncology Group Protocol 92-02: A Phase III Trial of the Duration of Elective Androgen Deprivation in Locally Advanced Prostate Cancer

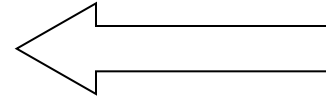


Randomized trials to test the use of Pelvic Irradiation in Prostate Cancer:

1 - RTOG 77-06 Stage A2, Stage B (1988)

445 analyzable patients

1. 65 Gy to the prostate
2. 45 Gy to the pelvis + 20 Gy boost to the prostate



2 - RTOG 94-13 Elevated PSA \leq 100 ng/ml (2003 - 2011) Estimated risk of nodal involvement > 15% 1323 randomized patients

1. Whole pelvic irradiation + Neoadjuvant Hormonal therapy
2. Prostate only RT + Neoadjuvant Hormonal therapy
3. Whole pelvic irradiation + Adjuvant Hormonal therapy
4. Prostate only RT + Adjuvant Hormonal therapy

3 - GETUG-01 (2007)

444 T1b - T3, N0 pNX, M0 patients

1. Pelvis + prostate RT (225 pts)
2. Prostate RT only (221 pts)

Randomized trials to test the use of Pelvic Irradiation in Prostate Cancer:

1 - RTOG 77-06 Stage A2, Stage B

Method of nodal evaluation:	Surgical	25%
	Lymphangiogram	75%

Treatment details Prostate and a portion of seminal vesicles
65 Gy

Maximum dose	72 Gy
Rectal and bladder dose not to exceed	

Pelvic nodal target volume	45 - 50 Gy	65 Gy
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5 year survival with local control	Prostate arm	88%
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Pelvic arm	90%
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5 year survival NED	Prostate arm	67%
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Pelvic arm	64%
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5 year survival without metastases	Prostate arm	84%
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Pelvic arm	83%
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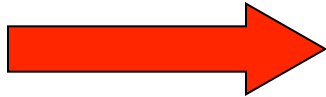
“Randomization was carried out with equal hormonal manipulation in both arms. It is conceivable that the **hormonal therapy may have masked evidence of distant metastases**”

Randomized trials to test the use of Pelvic Irradiation in Prostate Cancer:

1 - RTOG 77-06 Stage A2, Stage B (1988)
445 analyzable patients

1. 65 Gy to the prostate
2. 45 Gy to the pelvis + 20 Gy boost to the prostate

2 - **RTOG 94-13** Elevated PSA \leq 100 ng/ml (2003 - 2011)
Estimated risk of nodal involvement > 15%
1323 randomized patients

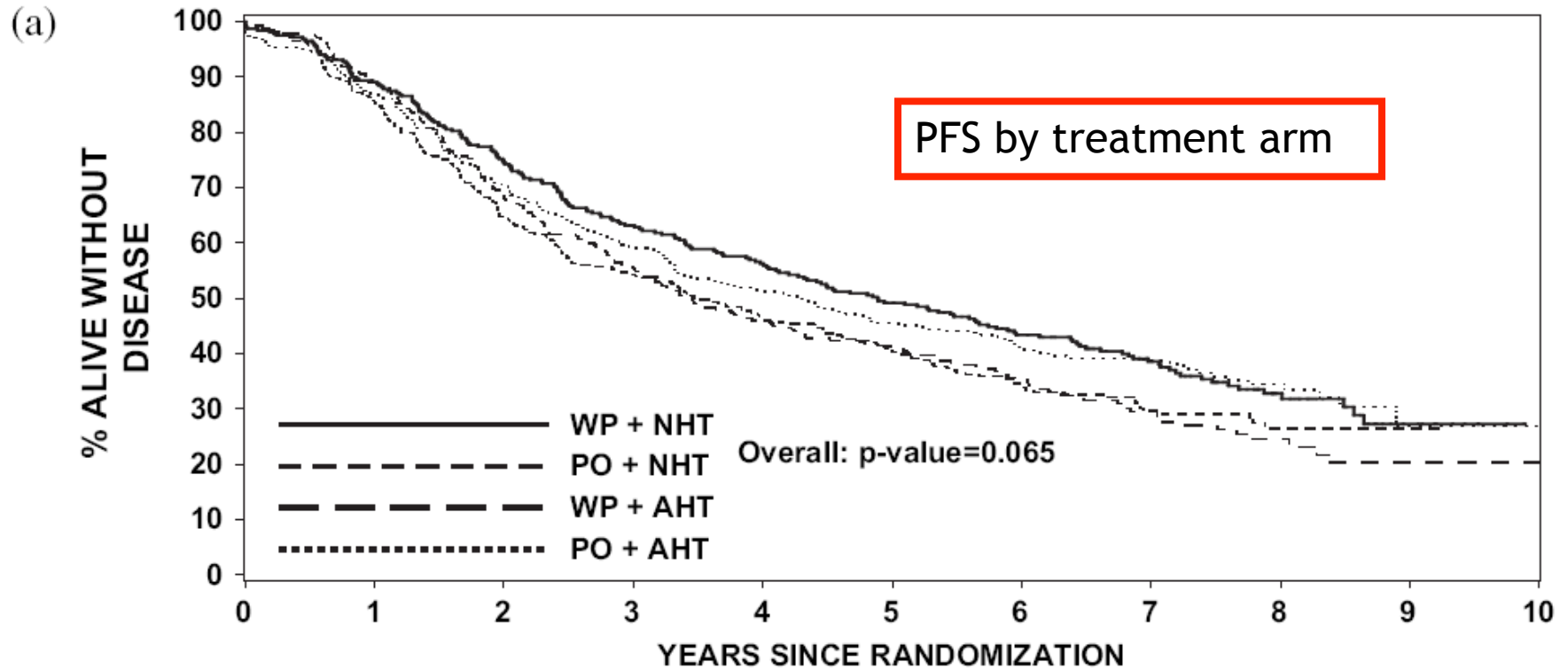


1. Whole pelvic irradiation + Neoadjuvant Hormonal therapy
2. Prostate only RT + Neoadjuvant Hormonal therapy
3. Whole pelvic irradiation + Adjuvant Hormonal therapy
4. Prostate only RT + Adjuvant Hormonal therapy

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1. Pelvis + prostate RT (225 pts)
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Randomized trials to test the use of Pelvic Irradiation in Prostate Cancer: RTOG 94-13



At Risk:

WP + NHT	198	110	9
PO + NHT	178	87	2
WP + AHT	177	92	6
PO + AHT	191	110	7

Randomized trials to test the use of Pelvic Irradiation in Prostate Cancer: RTOG 94-13

Primary endpoint for this study is PFS

Table 2. Progression-free survival*

Treatment arm	<i>n</i>	<i>p</i> *
WPRT + NHT	198/320	0.065
PORT + NHT	210/316	
WPRT + AHT	220/319	
PORT + AHT	199/320	
Pairwise comparison		
WPRT + NHT vs. PORT + NHT		0.066
WPRT + AHT PORT + AHT		0.022
PORT + NHT vs. WPRT + AHT		0.69
PORT + NHT PORT + AHT		0.15
WPRT + AHT vs. PORT + AHT		0.057

Abbreviations as in Table 1.

* *p* value is from the Log-rank for comparing progression-free survival curves.

Randomized trials to test the use of Pelvic Irradiation in Prostate Cancer: RTOG 94-13

Table 3. Overall survival

Treatment arm	<i>n</i>	<i>p</i>
WPRT + NHT	104/320	0.027*
PORT + NHT	99/316	
WPRT + AHT	130/319	
PORT + AHT	101/320	
Pairwise comparison		<i>p</i> value [†]
WPRT + NHT vs. PORT + NHT		0.9629
WPRT + AHT		0.019
PORT + AHT		0.80
PORT + NHT vs. WPRT + AHT		0.019
PORT + AHT		0.86
WPRT + AHT vs. PORT + AHT		0.01

Abbreviations as in Table 1.

* Log-rank test for comparing overall survival curves.

[†] *p* value is from the log rank for comparing overall survival curves.

Randomized trials to test the use of Pelvic Irradiation in Prostate Cancer: RTOG 94-13

Treatment Schema

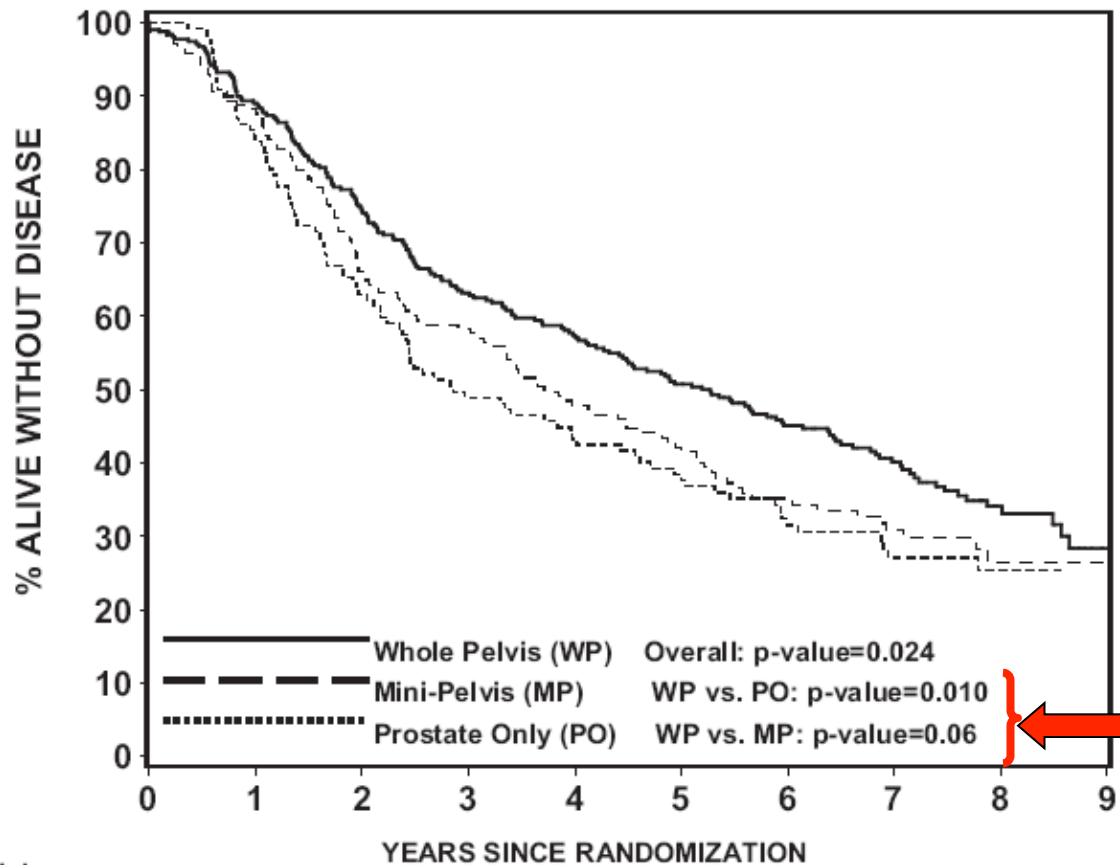
S T R A T I F I C A T I O N	1. Risk Group: “Favorable” High or “Unfavorable” Intermediate Risk: 1.GS=7-10 and T1c-T2b and PSA < 50 ng/ml or 2.GS=6, T2c-T4 or > 50% biopsies + & PSA <50 or 3.GS=6, PSA > 20 ng/ml and T1c-T2b	R E G I S T E R E	R A N D O M I Z E D	Arm 1: NADT + Prostate & SV vs Arm 2: NADT + Whole-Pelvic RT
	2. Type of RT Boost: IMRT vs Brachytherapy (HDR + PPI)			
	3. Duration of Androgen Deprivation Therapy Short Term vs Long Term ADT			

Fig. 4. Radiation Therapy Oncology Group 0924 schema. This study will evaluate the potential benefit of WPRT in patients with intermediate- risk prostate cancer and multiple adverse features or favorable high-risk disease. The primary endpoint is cause specific survival. GS = Gleason score; RT = radiotherapy; IMRT = intensity-modulated radiotherapy, HDR = high dose rate; PPI = permanent prostatic implant, NADT = neoadjuvant anti-androgen therapy; SV = seminal vesicles; WPRT = whole pelvic radiotherapy.

Randomized trials to test the use of Pelvic Irradiation in Prostate Cancer: RTOG 94-13

Whole-Pelvis, Mini-Pelvis or Prostate-Only: better results with a large volume in comparison to Prostate-Only RT?

(a) Protocol Definition



These patients were originally included in the same group (Prostate-Only and NHT) without a difference significant in terms of PFS and OS

At Risk:

	0	1	2	3	4	5	6	7	8	9
WP	309	274	227	189	167	142	109	78	35	10
MP	170	149	109	96	77	61	44	29	10	2
PO	131	109	81	61	54	47	34	22	10	0

Randomized trials to test the use of Pelvic Irradiation in Prostate Cancer: RTOG 94-13

Whole-Pelvis, Mini-Pelvis or Prostate-Only: better results with a large volume in comparison to Prostate-Only RT?

Table 3. Acute radiotherapy (RT) toxicities

Group	Whole-pelvis (<i>n</i> = 309)		Mini-pelvis (<i>n</i> = 170)		Prostate-only (<i>n</i> = 131)		<i>p</i> -value*
	<i>N</i>	Event (%)	<i>N</i>	Event (%)	<i>N</i>	Event (%)	
Grade 2 or higher							
GU [†]	309	97 (31.4%)	167 [‡]	63 (37.7%)	131	29 (22.1%)	0.016
GI [†]	309	144 (46.6%)	169 [§]	62 (36.7%)	131	27 (20.2%)	<0.001
Grade 3 or higher							
GU	309	12 (3.9%)	167 [‡]	10 (6.0%)	131	3 (2.3%)	0.27
GI	309	8 (2.6%)	169 [‡]	4 (2.4%)	131	1 (0.8%)	0.47

Abbreviations: GI = gastrointestinal; GU = genitourinary.

* χ^2 test.

[†] In pairwise comparisons, there was a statistically lower proportion of grade 2+ GU and GI toxicities in the Prostate-Only group compared to the Whole-Pelvis ($p < 0.05$) and Mini-Pelvis groups ($p < 0.05$).

[‡] Three cases had unknown or not reported GU toxicity information.

[§] One case excluded due to lack of treatment information.



Prostate Only Group
Lower Toxicity

Randomized trials to test the use of Pelvic Irradiation in Prostate Cancer:

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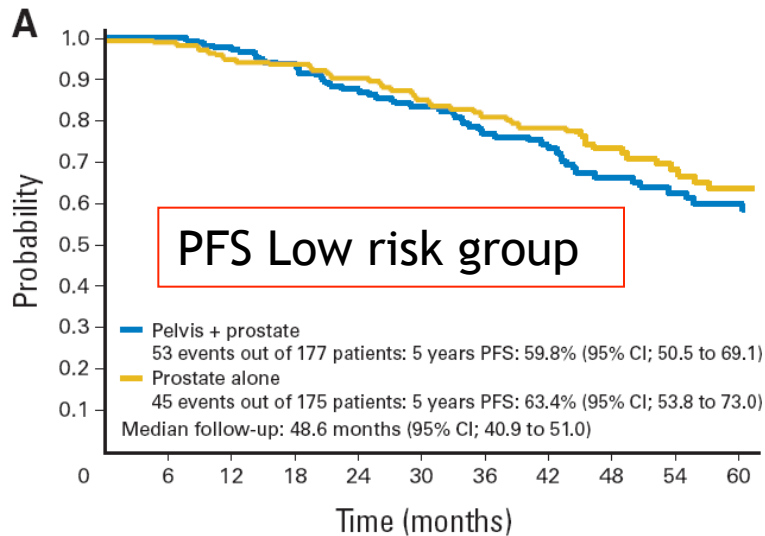
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Estimated risk of nodal involvement > 15%
1323 randomized patients
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- 3 - **GETUG-01 (2007)**
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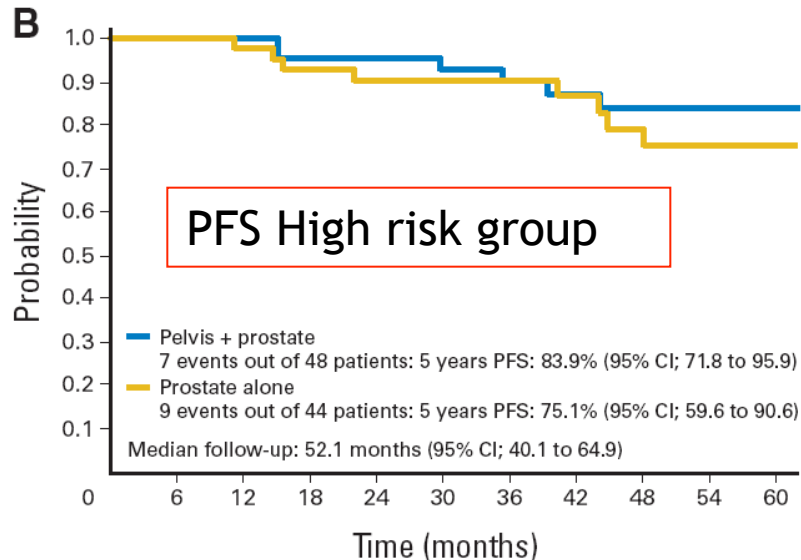


Is there a role for Pelvic Irradiation in localized prostate adenocarcinoma?

Preliminary results of GETUG-01



No. of patients at risk	0	6	12	18	24	30	36	42	48	54	60
Pelvis + prostate	168	168	167	165	162	158	153	147	140	132	124
Prostate alone	161	161	160	158	155	151	146	140	133	125	117



No. of patients at risk	0	6	12	18	24	30	36	42	48	54	60
Pelvis + prostate	47	47	46	45	44	43	42	41	40	39	38
Prostate alone	41	41	40	39	38	37	36	35	34	33	32

PFS	Low risk	High risk
	Rt only	Rt + AD
	60% - 63%	75% - 84%

Is there a role for Pelvic Irradiation in localized prostate adenocarcinoma? Preliminary results of GETUG-01

In this trial, pelvic irradiation did not lead to any improvement in PFS. With a median follow-up time of 12 years, the first randomized trial assessing pelvic irradiation (RTOG 7706) did not demonstrate any significant benefit for pelvic irradiation on clinical end points.^{23,24} This trial has been criticized for including men with low risk of nodal involvement and for its use of relatively low radiation doses and no hormonal therapy. RTOG 9413 addressed the same question for patients at highest risk of nodal disease (> 15%) using hormonal therapy. With a 59.5-month median follow-up time, a significant benefit for whole pelvis irradiation was seen in terms of 4-year PFS. The most important benefit for whole pelvis irradiation was reported when hormonal treatment was used in a neoadjuvant and concomitant setting. These later results were confirmed in a subsequent subset analysis with a 70.8-month median follow-up time.¹