Strategies of Radiotherapy for Intermediate- to High-Risk Prostate Cancer

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How to treat with radiotherapy for more efficacies in intermediate- to high risk prostate cancer ?

- Dose escalation
- Hypofractionation
- Prophylactic irradiation to the whole pelvis
- In combination with hormone therapy
- In combination with hormone and chemotherapy

NCCN Guideline 2015

- **Intermediate Risk**

Expected years to live	Treatment options
<10 years	• Observation
	• Radiation therapy ◦ EBRT ± brachytherapy ± ADT for 4–6 months, or ◦ LDR brachytherapy alone for low-volume disease
≥10 years	• Surgical treatment ◦ Radical prostatectomy, or ◦ Radical prostatectomy + PLND if ≥2% risk of cancer in lymph nodes
	• Radiation therapy ◦ EBRT ± brachytherapy ± ADT for 4–6 months, or ◦ LDR brachytherapy alone for low-volume disease

- **High Risk and Very High Risk**

Treatment options
• Radiation therapy ± ADT ◦ EBRT + ADT for 2–3 years, or ◦ EBRT+ brachytherapy ± ADT for 2–3 years

EAU Guideline 2015

- RT for intermediate risk

	GR
In intermediate- risk PCa the total dose should be 76-78 Gy, in combination with short-term ADT (4-6 mo).	A

- RT for high risk

	GR
In patients with **high-risk localised** PCa, the total dose is 76-78 Gy in combination with long-term ADT (2-3 yrs is recommended).	A
In patients with **locally advanced cN0** PCa, radio-therapy must be given in com-bination with long-term ADT (2-3 yrs is recommended).	A

Randomised Trials on Dose Escalation in Localized Prostate Cancer

Trial	n	PCa condition	Radiotherapy Dose	Follow-up	Outcome	Results
MD Anderson study 2011 [391] Int J Radiat Oncol Biol Phys 2011	301	T1-T3, N0, M0, PSA 10 ng/mL vs. PSA > 10 ng/mL	70 vs.78 Gy	Median 9 years	Disease specific mortality (DSM) vs. other cause of death	High risk / PSA >10 16% DSM @ 70 Gy 4% DSM @ 78 Gy (p = 0.05) Higher risk 15% DSM @ 70 Gy 2% DSM @ 78 Gy (p = 0.03)
PROG 95-09 study [392] J Clin Oncol 2010	393	T1b-T2b PSA 15 ng/mL 75% GLS < 6	70.2 vs.79.2 Gy including proton boost 19.8 vs. 28.8 Gy	Median 8.9 years for survivors	10-year ASTRO Biochemical failure (BF)	All patients: 32% BF @ 70.2 Gy 17% BF @ 79.2 Gy (p < 0.0001) Low-risk patients: 28% BF @ 70.2 Gy 7% BF @ 79.2 Gy (p < 0.0001)
MRC RT01 study [388] Lancet Oncol 2014	843	T1b-T3a, N0, M0 PSA < 50 ng/mL neoadjuvant HT	64 vs. 74 Gy	Median 10 years	Biochemical progression free survival (BFS); OS	43% BFS @ 64 Gy 55% BFS @ 74 Gy (p = 0.0003) 71% OS both groups (p = 0.96)
Dutch randomised phase III trial [394]	664	T1b-T4 143 pts. with (neo)adjuvant HT	68 vs. 78 Gy	Median 51 mo	Freedom from biochemical- or clinical failure (FFF @ 5 years)	54% FFF @ 68 Gy 64% FFF @ 78 Gy (p = 0.02)

To date, no trials have shown that dose escalation results in an OS benefit.

Moderate hypofractionation (2.5 - 4 Gy per fractions)

Table 1 – Phase 3 randomized trials of moderate hypofractionation for intact prostate cancer

Study	Median FU, mo	Risk, GS, or NCCN	Technique	Regimen	BED, Gy	*n*	Outcome	Toxicity
Lukka et al. [15]	68	60% GS ≤6 31% GS 7 9% GS 8–10	3DCRT No IGRT	52.5 Gy/20 fx	62	466	5 yr FFBF 40% (NS)	Gr ≥3 2% (NS)
				66 Gy/33 fx	66	470	5 yr FFBF 43%	Gr ≥3 1%
Yeoh et al. [17]	90	n.s.	2D/3DCRT No IGRT	55 Gy/20 fx	66.8	108	7.5 yr FFBF 53% ($p < 0.05$)	Late GU; HR: 1.58 (95% CI, 1.01–2.47) favoring hypofractionation
				64 Gy/32 fx	64	109	7.5 yr FFBF 34%	
Dearnaley et al. [18]	51	n.s.	3D/IMRT No IGRT 3–6 mo ADT	57 Gy/19 fx	73.4	151	n.s.	Gr ≥2 GU 0% (NS) Gr ≥2 GI 1% (NS)
				60 Gy/20 fx	77	153		Gr ≥2 GU 2% Gr ≥2 GI 4%
				74 Gy/37 fx	74	153		Gr ≥2 GU 2% Gr ≥2 GI 4%
Kuban et al. [14]; Hoffman et al. [19]	60	28% low 71% intermediate 1% high	IMRT IGRT 21% ADT	72 Gy/30 fx	80.2	102	5 yr FFBF 96% (NS)	5 yr Gr ≥2 GU 16% (NS) 5 yr Gr ≥2 GI 10% (NS)
				75.6 Gy/42 fx	71.4	101	5 yr FFBF 92%	5 yr Gr ≥2 GU 17% 5 yr Gr ≥2 GI 5%
Arcangeli et al. [12,13]	70	26% GS ≤7 74% GS >7	3DCRT No IGRT 100% 9 mo ADT	62 Gy/20 fx	81.4	83	5 yr FFBF 85% ($p = 0.065$) *p ss for GS ≥4 + 3	3 yr Gr ≥2 GU 16% (NS) 3 yr Gr ≥2 GI 17% (NS)
				80 Gy/40 fx	80	85	5 yr FFBF 79%	3 yr Gr ≥2 GU 11% 3 yr Gr ≥2GI 14%
Pollack et al. [16]	68	34% GS ≤6 47% GS 7 19% GS 8–10	IMRT IGRT	70.2 Gy/26 fx	84	151	5 yr BCDF 23% (NS)	5 yr Gr ≥2 GU 13% ($p = 0.16$) 5 yr Gr ≥2 GI 9% (NS)
				78 Gy/36 fx	78	152	5 yr BCDF 21%	5 yr Gr ≥2 GU 13% 5 yr Gr ≥2 GI 9%

In low-and intermediate-risk it is still unclear whether moderate hypofractionation will ultimately prove to provide similar biochemical control, distant disease survival and cancer-specific survival as standard fractionation.

Koontz et al. Eur Urol 68; 683-691, 2015

Extreme hypofractionation (5-10 Gy in 4-7 fractions)

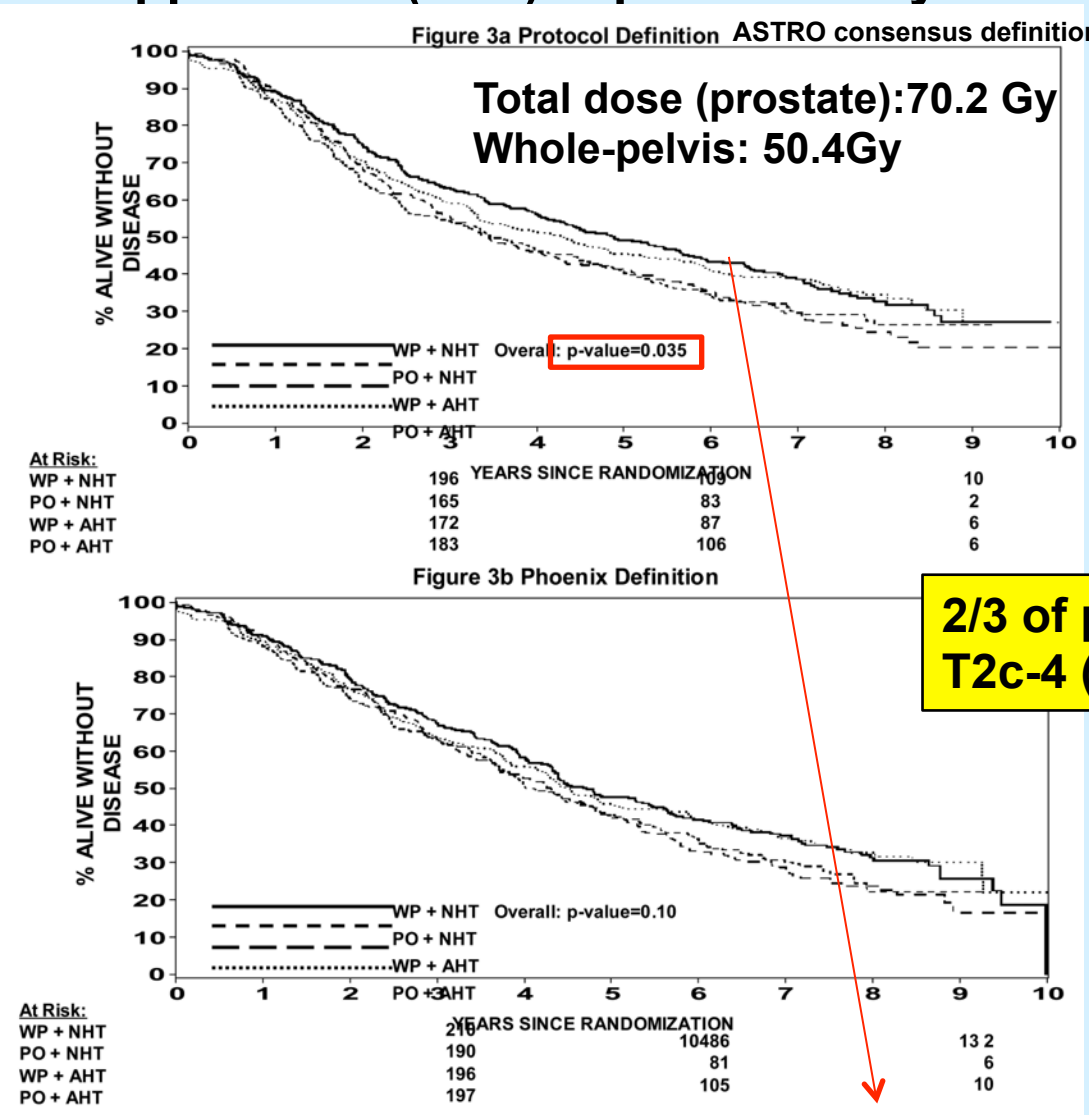
Table 2 – Prospective studies of extreme hypofractionation for intact prostate with at least 50 participants

	n	Median FU, mo	Risk, NCCN	Technique	Regimen	BED, Gy	Outcome	Toxicity
Aluwini et al. [46]	162	28	Low/intermediate	n.s.	38 Gy/4 fx	119.6	3 yr BC 98%	Gr 2 GU 15% Gr 2 GI 3%
Bolzicco et al. [27]	100	36	41% low 42% intermediate 17% high	Robotic IGRT	35 Gy/5 fx 29% ADT	85	BC 96%	Gr 1/2/3 GU 4%/3%/1% Gr 1/2/3 GI 2%/1%
Chen et al. [47]	100	28	37% low 55% intermediate 8% high	Robotic IGRT	35–36.25 Gy/5 fx 11% ADT	85-90.6	2 yr BRFS 99%	2 yr Gr ≥2 GU 31% 2 yr Gr ≥2 GI 1%
D'Alimonte et al. [48]	84	50	100% low	IMRT/IGRT	35 Gy/5 fx	85	BC 98%	Gr 2/≥3 GU 5/1% Gr 2/≥3 GI 5/1%
Fuller et al. [39]	260	20	45% low 55% intermediate	n.s.	38 Gy/4 fx	119.6	3 yr BRFS 98%	Gr 3 GU 2% (any Gr 44%) Gr 3 GI 0% (any Gr 11%)
Katz and Kang [24]	515	54	67% low 26% intermediate 7% high	Robotic IGRT	35–36.25 Gy/5 fx	85-90.6	6 yr FFBF 97% 92% 70%	Gr ≥2 GU 9% Gr ≥2 GI 4%
King et al. [34]	67	32	100% low	Robotic IGRT	36.25 Gy/5 fx	90.6	4 yr BRFS 94%	Gr ≥2 GU 7% Gr ≥2 GI 12%
Loblaw et al. [25]	84	55	100% low	IMRT/IGRT	35 Gy/5 fx	85	5 yr BC 98%	5 yr Gr ≥2 GU 5% 5 yr Gr ≥2 GI 7%
Meier et al. [38,49]	129	30	100% intermediate	Robotic IGRT	40 Gy/5 fx No ADT	108.8	3 yr BRFS 99%	Gr 2 GU 10% Gr 2 GI 2%
Menkarios et al. [29]	80	33	100% low	IMRT/IGRT	45 Gy/5 fx	135	3 yr BC 97%	Gr ≥2 GU 14% Gr ≥2 GI 16%
Ouon et al. [50]	84	18	100% low	IMRT/IGRT	35 Gy/5 fx	85	n.s.	Gr 2 GU 2% Gr 2 GI 5%

- **Only low risk and selected intermediate-risk patients have been studied.**
- **Biochemical control at 5ys in the low-risk are similar to a high dose IMRT series.**
- **However, moderate- to high-grade acute toxicities ranges 10-20% high.**

Kotecha et al. Eur Urol 68, 658-669, 2015

An Update of the Phase trial comparing whole-pelvis (WP) to prostate only (PO) radiotherapy and neoadjuvant to adjuvant total androgen suppression (TAS): Updated analysis of RTOG 94-13



2/3 of pts had clinical T2c-4 (High risk)

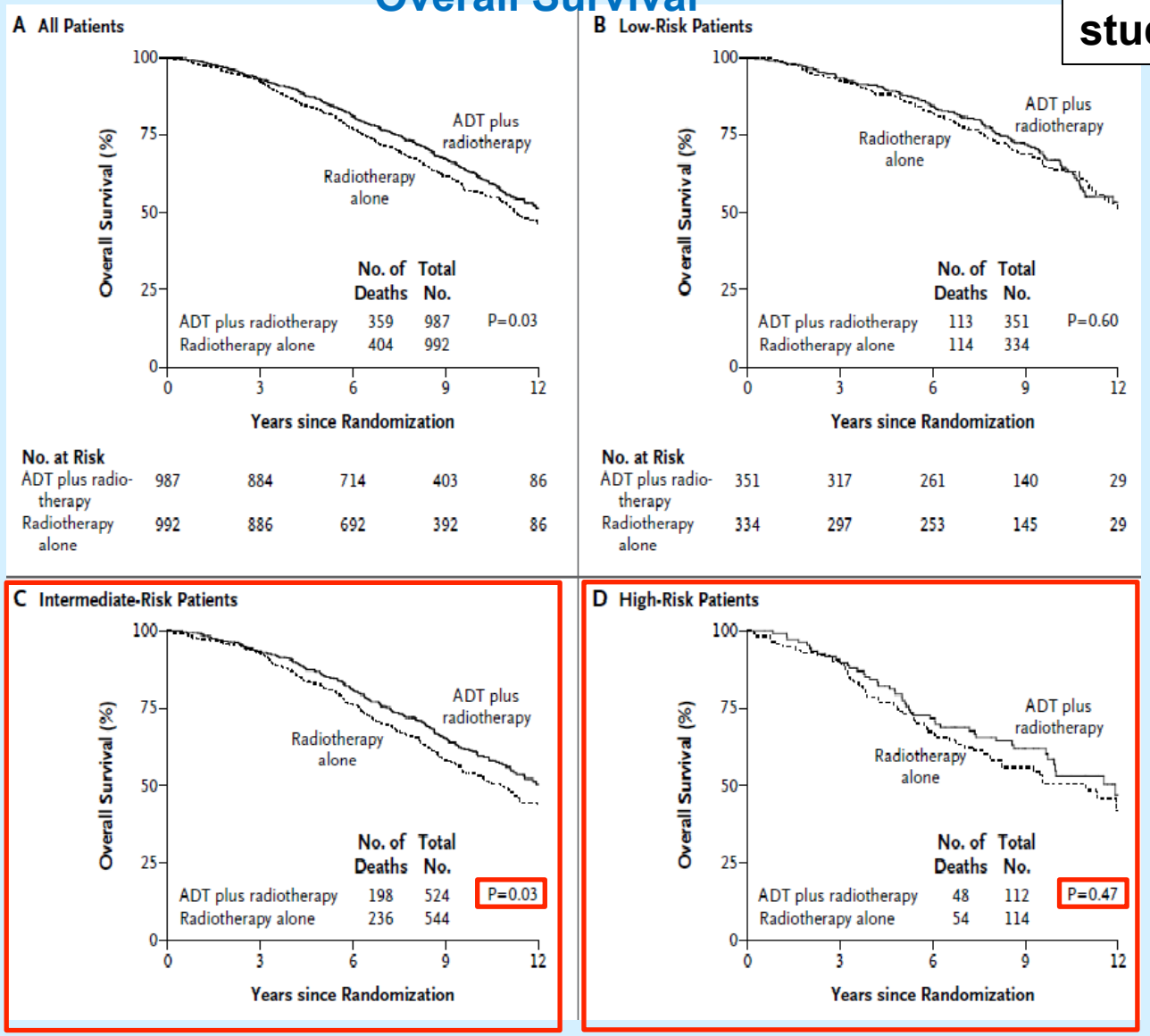
Significant difference in PFS in favor of the WP+NHT arm over PO+NHT and WP + AHT

Lawton et al. Int J Radiat Oncol Biol Phys 69: 646-55, 2007

EBRT and short-term androgen deprivation (4 months of total androgen suppression) is favorable OS for intermediate risk

RTOG 94-08 study

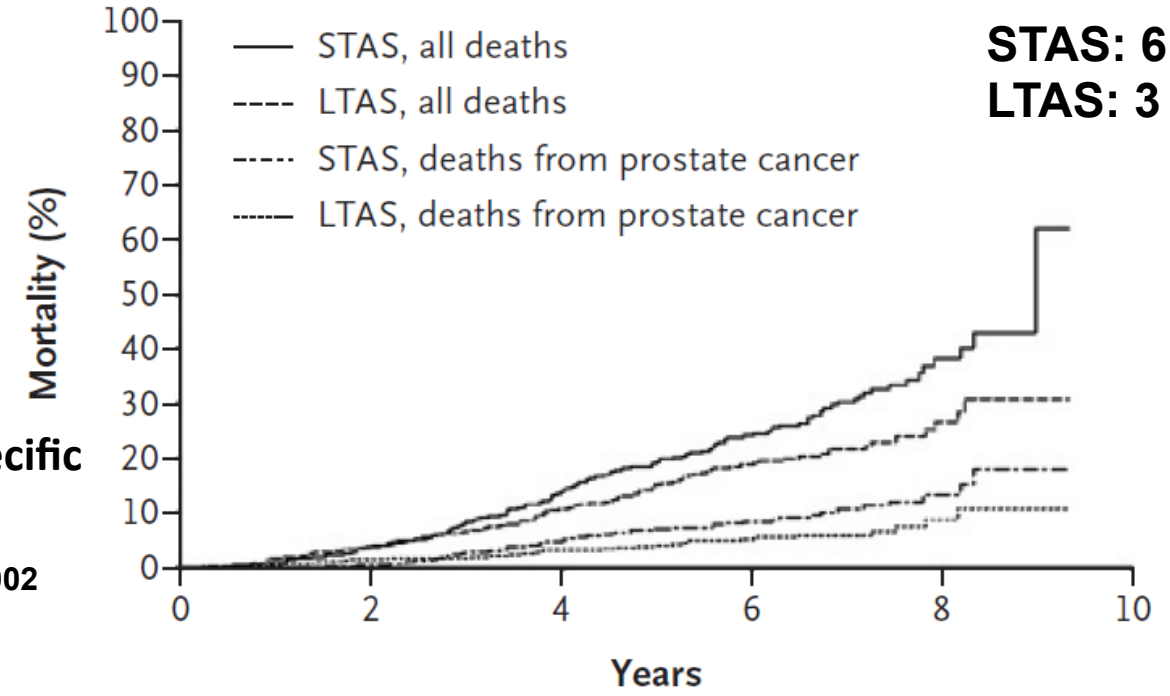
Overall Survival



Jones et al. N Engl J Med 365; 107-18, 2011

Overall and cancer-specific mortality in duration of ADT

EORTC 22961 trial



STAS: 6 ms ADT
LTAS: 3 ys ADT

- **The 5-ys Cancer-specific mortality**
  - **STAS: 4.7% > P=0.002**
  - **LTAS: 3.2%**

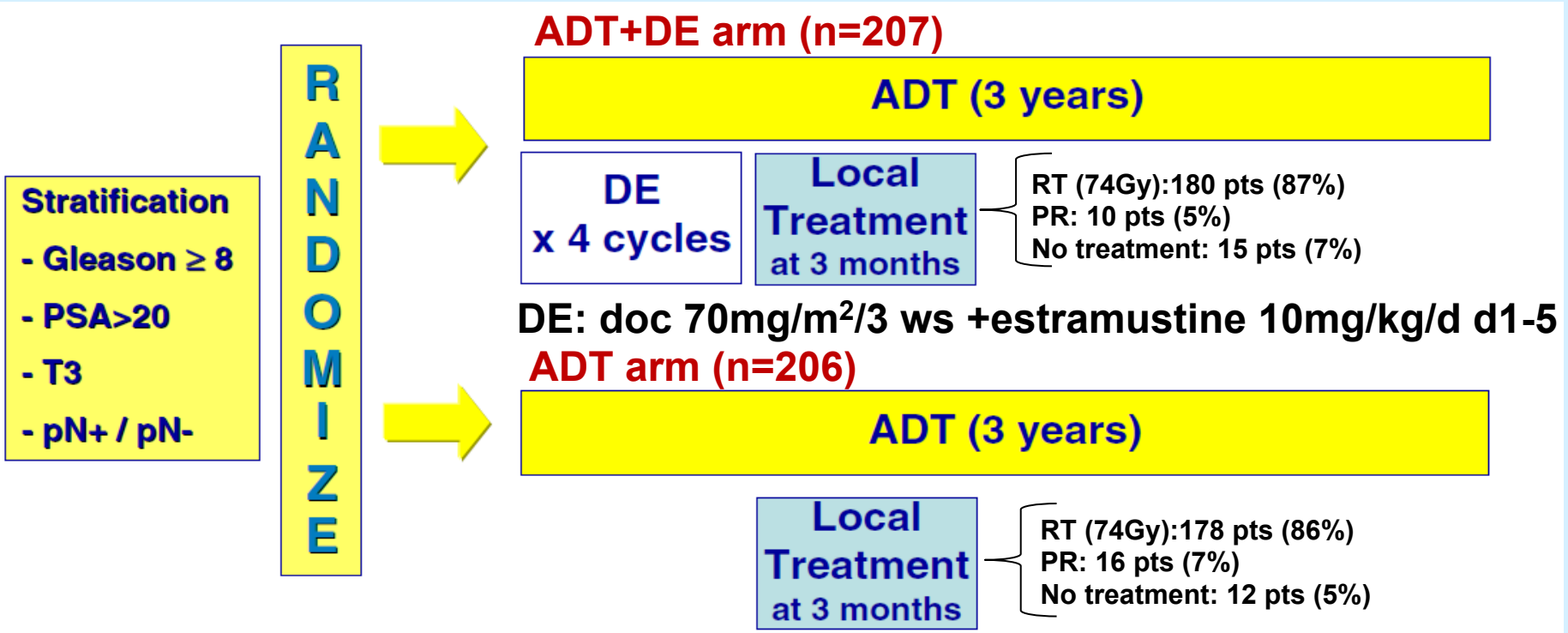
No. at Risk						No. of Events
STAS, all deaths	483	454	388	231	43	132
LTAS, all deaths	487	454	407	249	50	98
STAS, deaths from prostate cancer	483	454	388	231	43	47
LTAS, deaths from prostate cancer	487	454	407	249	50	29

- **The combination of RT plus LTAS provides superior survival as compared with RT plus STAS in the treatment of locally advanced prostate cancer.**

Balla et al. N Engl J Med 360; 2516-27, 2009

A phase III trial of docetaxel–estramustine in high-risk localised prostate cancer: GETUG 12 trial

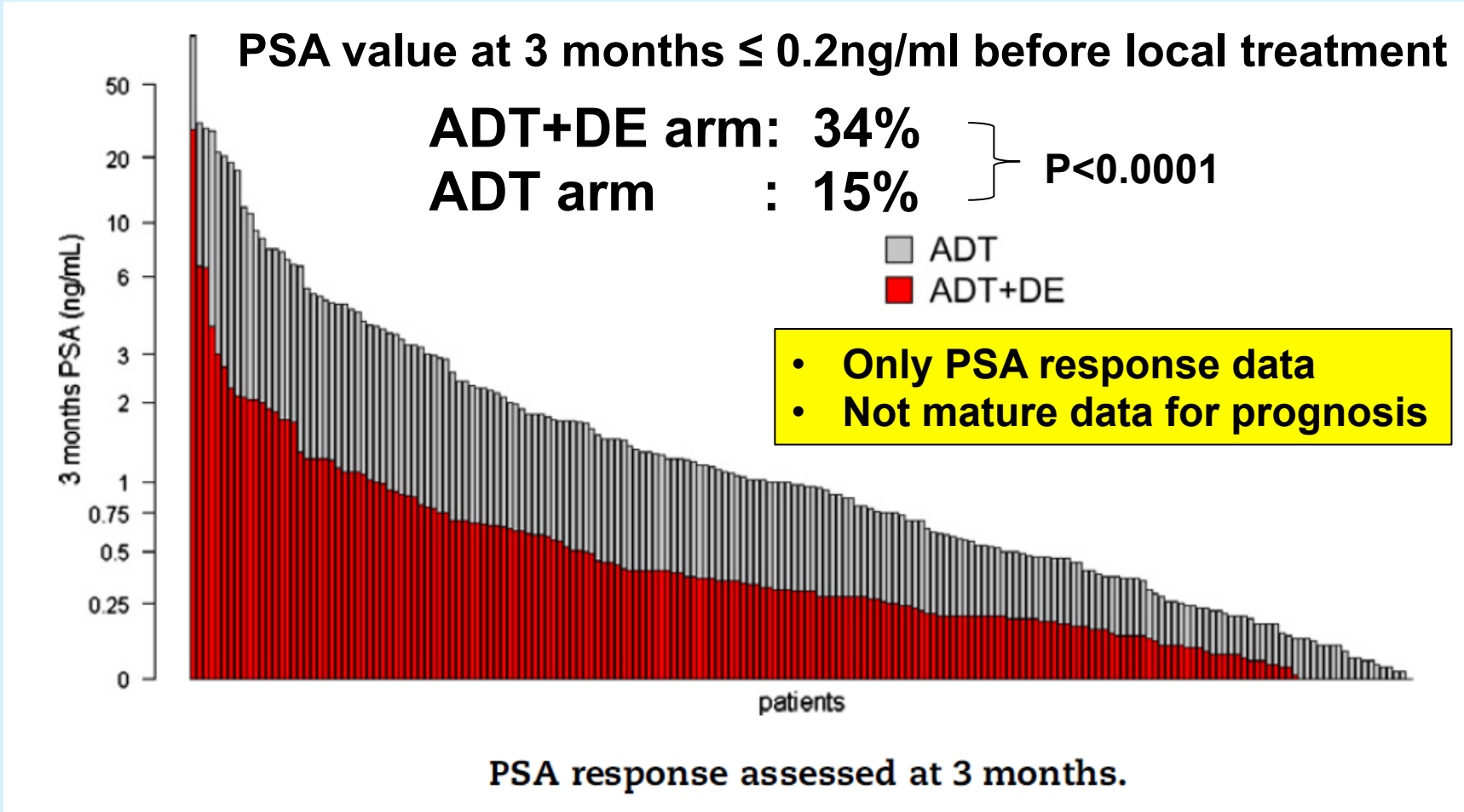
French Group d'Etude des Tumeurs Uro-Genitales



Trial design.

Fizazi et al. Eur J Cancer 48; 209-217, 2012

A phase III trial of docetaxel–estramustine in high-risk localised prostate cancer: GETUG 12 trial



Fizazi et al. Eur J Cancer 48; 209-217, 2012

A phase III trial of docetaxel–estramustine in high-risk localised prostate cancer: GETUG 12 trial

Table 4 – Grade 3–4 toxicity in the chemotherapy arm.

	ADT + DE arm (n = 205)
Neutropenia	
Grade 3	29 (14%)
Grade 4	27 (13%)
Febrile neutropenia	5 (2%)
Grade 3–4 infection	4 (2%)
Grade 3–4 Thrombosis	5 (2%)
Grade 3 Diarrhoea	10 (5%)
Grade 3 Nausea	5 (2%)
Grade 3 Fatigue	5 (2%)
Grade 3 Alopecia	4 (2%)
Grade 3 Cardiac	2 (1%)
Grade 3 Skin	2 (1%)

Severe hematological toxicities often occurred.

Fizazi et al. Eur J Cancer 48; 209-217, 2012

Int Urol Nephrol (2010) 42:81–88
DOI 10.1007/s11255-009-9580-7

UROLOGY - ORIGINAL PAPER

Neoadjuvant LHRH analog plus estramustine phosphate combined with three-dimensional conformal radiotherapy for intermediate- to high-risk prostate cancer: a randomized study

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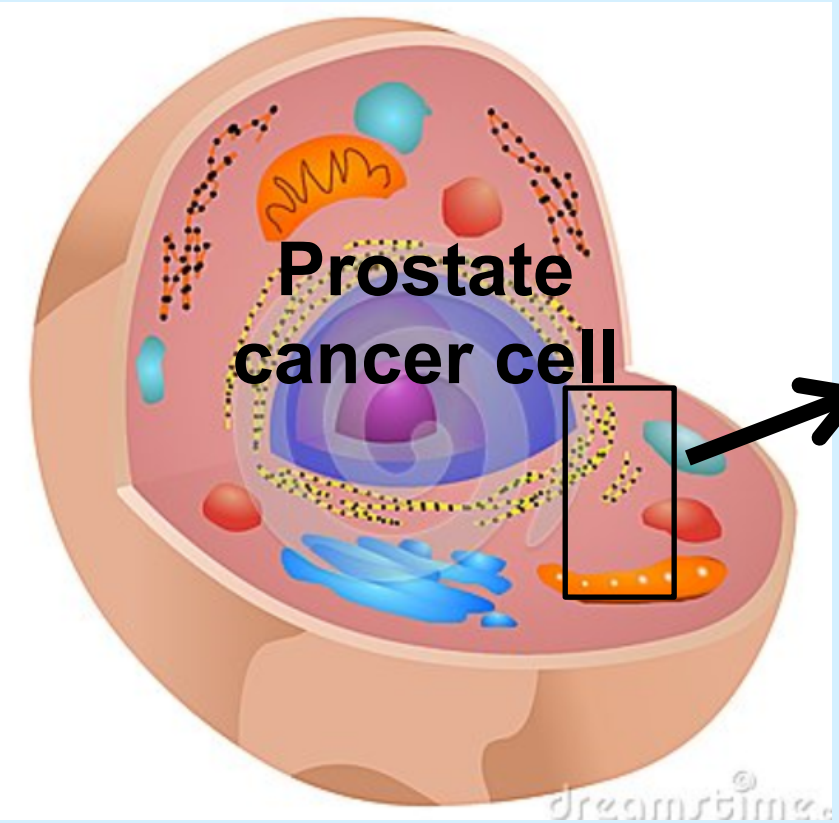
Abstract

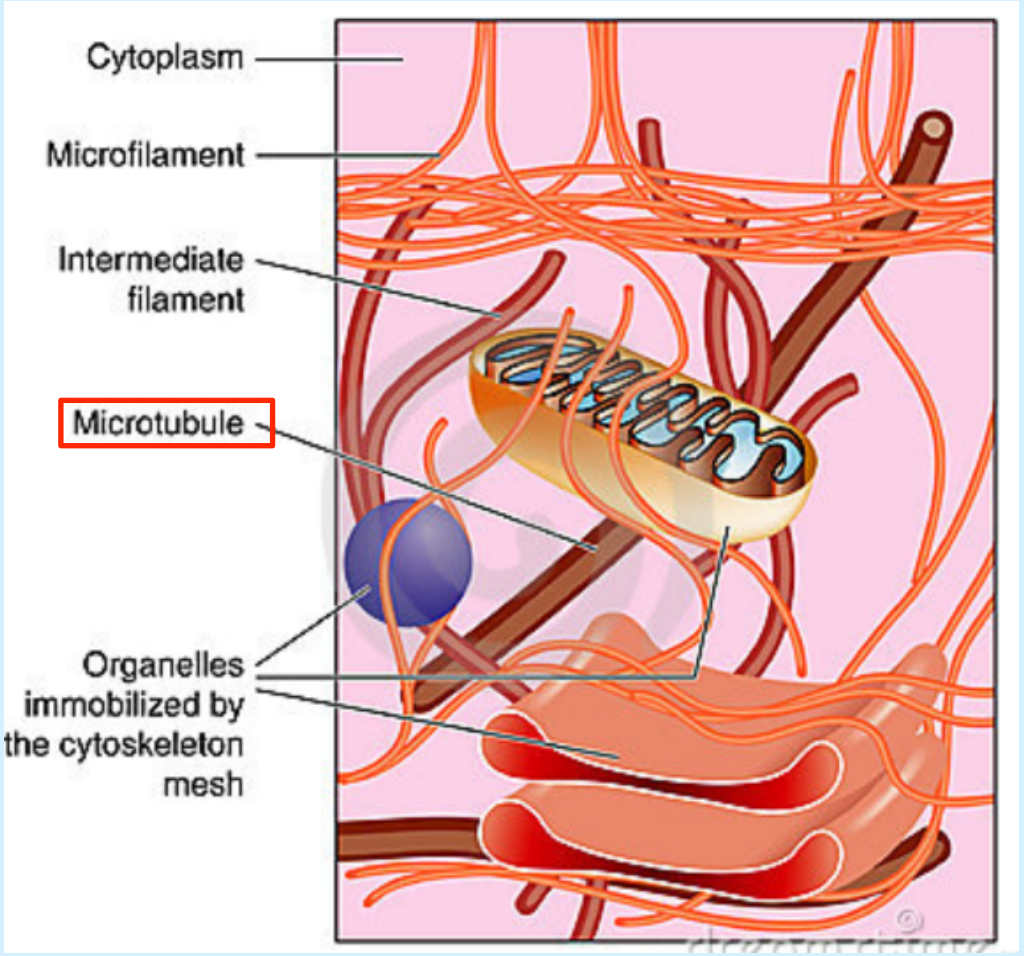
Objective The objective of this study is to assess the safety and efficacy of a treatment regimen comprising neoadjuvant conventional androgen deprivation therapy (ADT) plus estramustine phosphate (EMP) combined with three-dimensional conformal radiotherapy (3D-CRT) for patients with intermediate- to high-risk prostate cancer.

Results The median duration of follow-up was 27.1 months. None of the patients died during the follow-up period, but three patients in the LHRH group developed distant metastasis. The 4-year PSA relapse-free survival outcomes for the EMP group and LHRH group were 61.2 and 49.4%, respectively ($P = 0.04$). Multivariate Cox regression model analyses of the pretreatment PSA level (>20 ng/ml

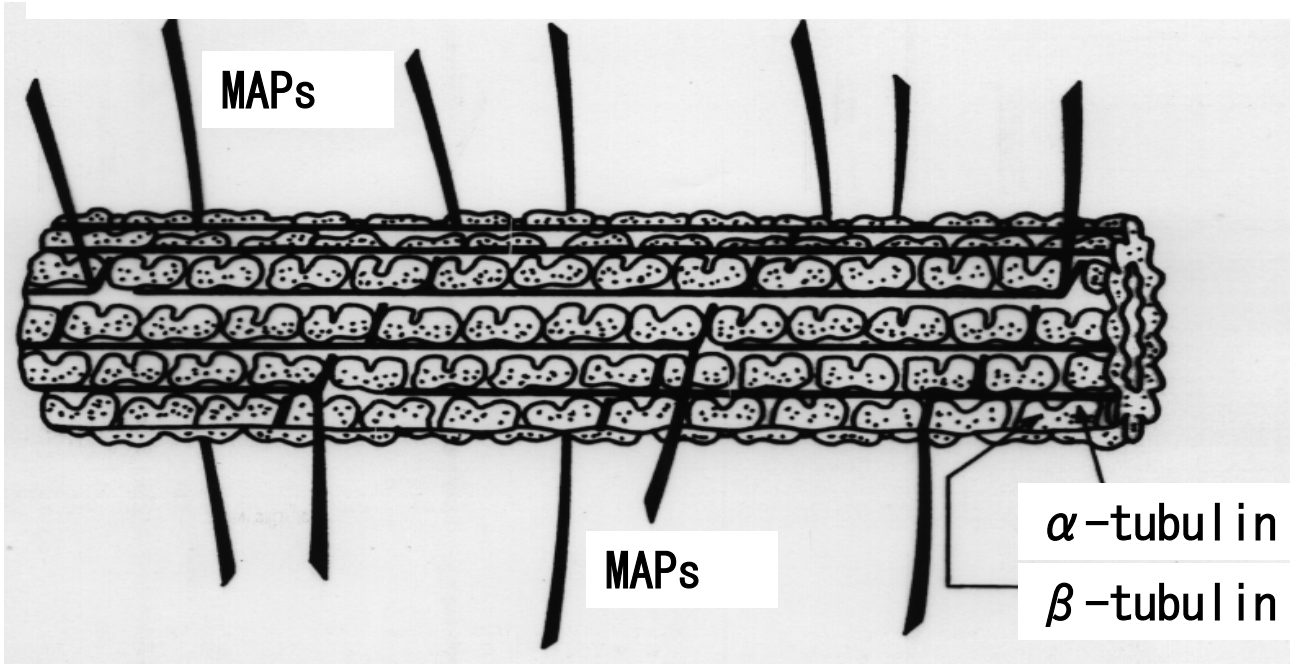
Mechanisms of action in estramustine phosphate (EMP)

- Hormonal action
- Cytotoxic action





Structure of Microtubules



EMP binds:

- –Microtubule associated proteins (MAPs)
- –[illegible] tubulin
- –[illegible] tubulin at a site near, but not overlapping the taxane site

Taxanes bind: [illegible] tubulin at sites distinct from estramustine binding

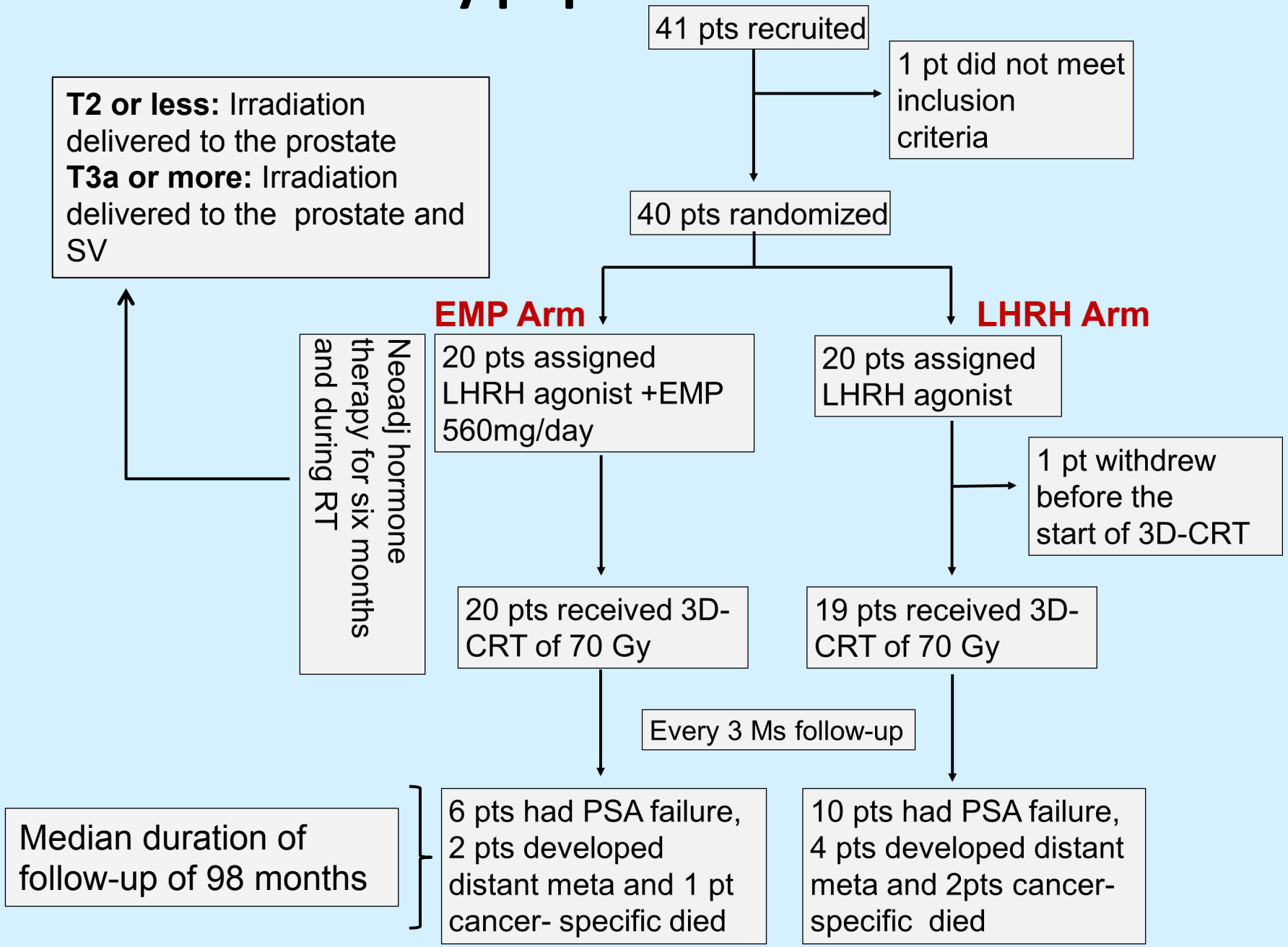
Why is EMP in combination with RT benefit for the treatment of prostate cancer?

- Cell kinetic studies have shown that EMP causes G2-phase arrest. （Hartley-Asp B et al. Prostate 5; 93-100, 1984）
- Cells are most radiosensitive in the G2/M phase. （Kim et al. Int J Radiat Oncol Biol Phys 29: 555-557 1994）
- EMP enhances radiation-induced cytotoxicity in DU-145 cells in culture and in transplanted into nude mice （Eklov et al. Prostate 29; 39-45, 1994）

↓

EMP is considered to have radiosensitizing properties

Study population flowchart



Patient characteristics

	EMP G ($n = 20$)	LHRH G ($n = 19$)	P-value
Median age, years (range)	72 (61–86)	72 (63–79)	0.627
PSA, ng/ml (%)			
<10	7 (35)	5 (26)	0.8186
10–20	5 (25)	6 (32)	
>20	8 (40)	8 (42)	
Clinical stage (%)			
T2 or less	9 (45)	12 (63)	0.5188
T3a	5 (25)	3 (16)	
T3b	6 (30)	4 (21)	
Gleason score (%)			
6 or less	2 (10)	7 (37)	0.1248
7	12 (60)	7 (37)	
8–10	6 (30)	5 (26)	
NCCN (%)			
Intermediate	8 (40)	9 (47)	0.7512
High	12 (60)	10 (53)	
Median PSA nadir after treatment, ng/ml (range)	0.04 (0.04–0.47)	0.12 (0.04–13.17)	0.0058
Median time from initial treatment to PSA nadir, m (range)	6.0 (4.4–14.2)	9.4 (2.8–36.1)	0.0460

Median duration of follow-up: 27.1 months (range: 5.8-.48.3 Months)

Hirano et al. Int Urol Nephrol 42; 81-88, 2010

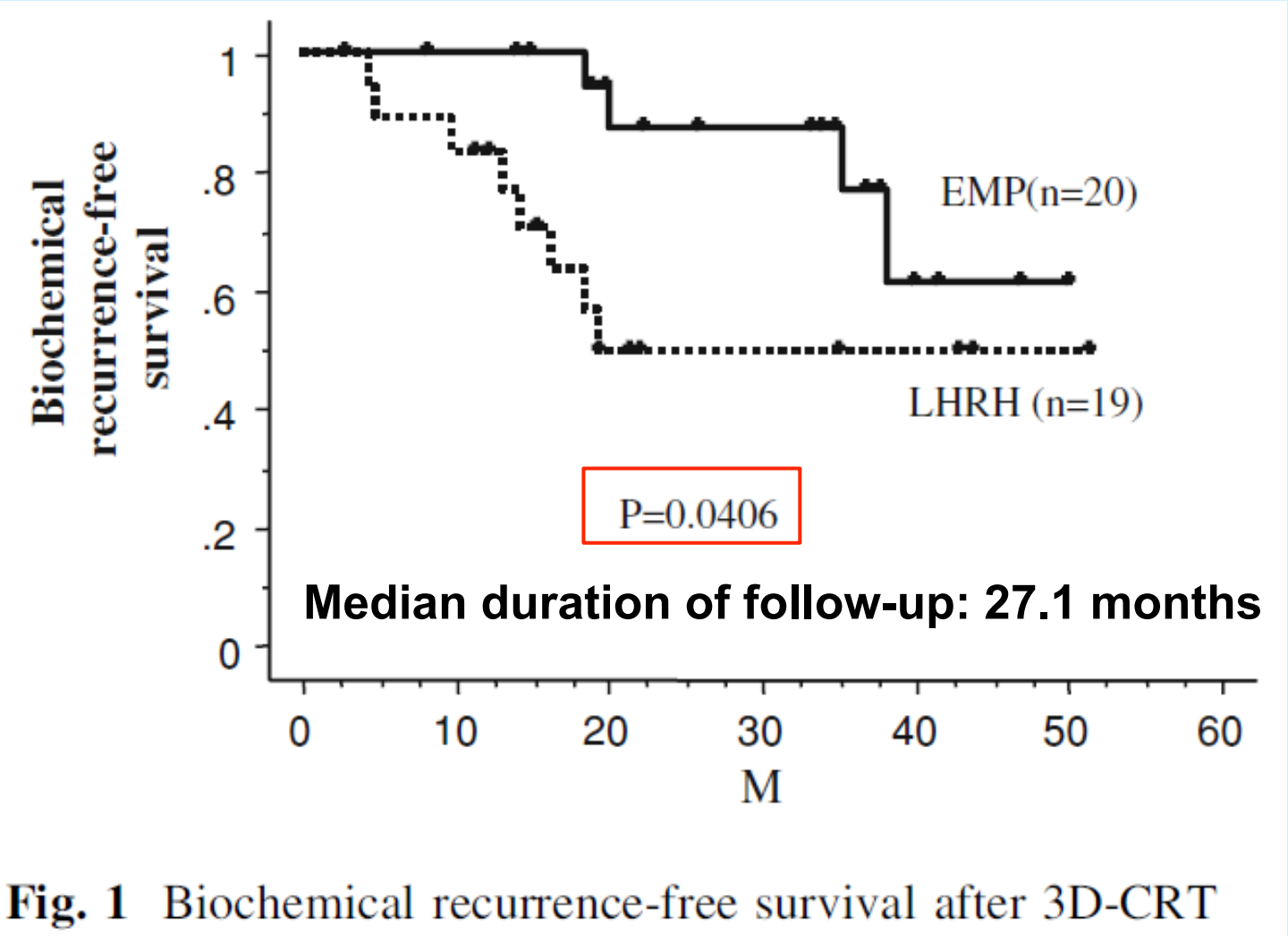


Fig. 1 Biochemical recurrence-free survival after 3D-CRT

Hirano et al. Int Urol Nephrol 42; 81-88, 2010

Correlation between PSA relapse and variables by Cox proportional hazards regression analysis

Table 2 Univariate and multivariate Cox proportional hazards regression analysis of variables in relation to the risk of PSA relapse as an indicator of prostate cancer progression

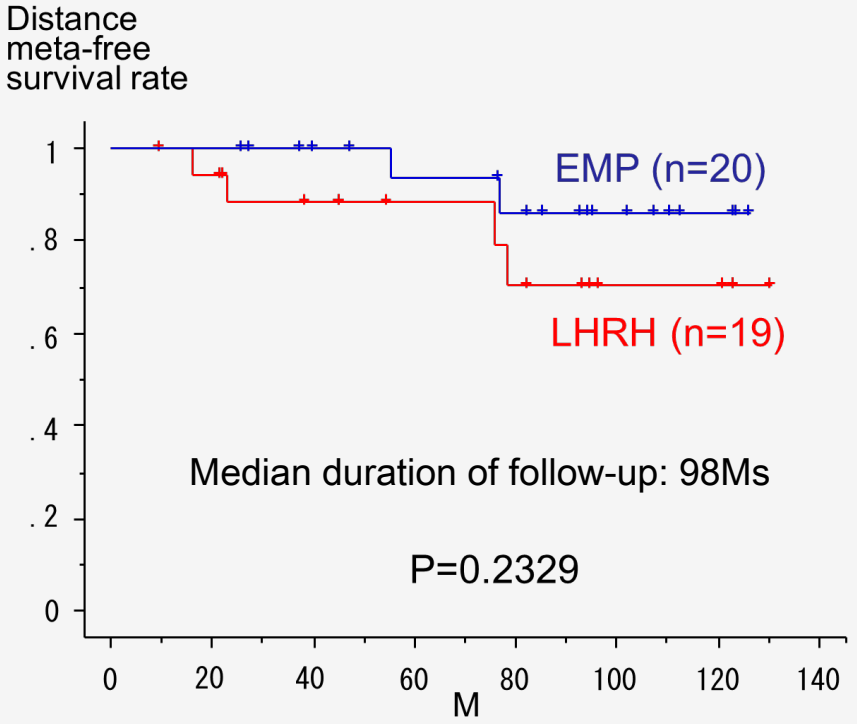
Variables	Relative risk (95%CI)	*P*-value
Univariate analysis		
Pretreatment PSA (>20, $n = 16$ vs. 20 or less, $n = 23$)	3.660 (1.099–12.185)	0.0345
Tumor stage (T3, T4, $n = 18$ vs. T2 or less, $n = 21$)	2.545 (0.764–8.475)	0.1279
Tumor grade (G 8–10, $n = 11$ vs. G7 or less, $n = 28$)	3.620 (1.153–11.368)	0.0275
NCCN classification (high, $n = 19$ vs. intermediate, $n = 17$)	4.265 (0.933–19.499)	0.0614
Modality (LHRH, $n = 19$ vs. EMP + LHRH, $n = 20$)	3.409 (1.017–11.419)	0.0468
Multivariate analysis		
Pretreatment PSA (>20, $n = 16$ vs. 20 or less, $n = 23$)	3.843 (1.003–14.722)	0.0495
Tumor grade (G 8–10, $n = 11$ vs. G7 or less, $n = 28$)	4.289 (1.093–16.824)	0.0368
Modality (LHRH, $n = 19$ vs. EMP + LHRH, $n = 20$)	8.009 (1.867–34.361)	0.0051

Median duration of follow-up: 27.1 months

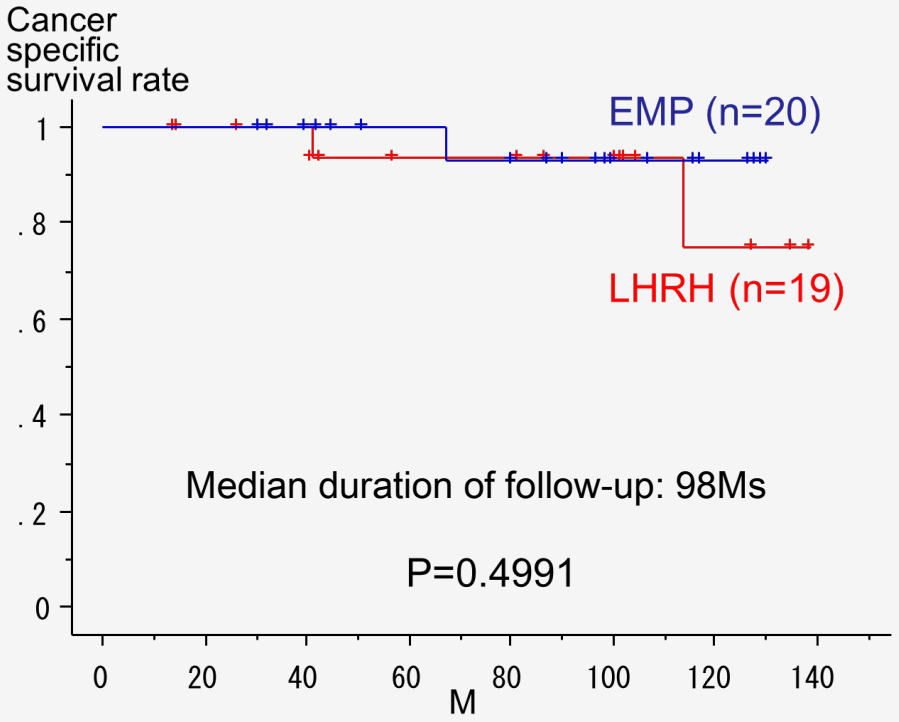
Hirano et al. Int Urol Nephrol 42; 81-88, 2010

Distant metastasis-free and cancer-specific survival at a median duration of follow-up of 98 months (long follow-up duration)

Distance metastasis-free survival after 3D-CRT



Cancer-specific survival after 3D-CRT



The combination of neoadjuvant ADT + EMP combined with RT did not contribute to distance metastasis-free and cancer-specific survival benefits in the long follow-up period.

Table 3 Adverse events (%)

Events	EMP G ($n = 20$)	LHRH G ($n = 19$)
Gynecomastia		
Grade 1	9 (45)	
Gastrointestinal		
Anorexia		
Grade 1	5 (25)	2 (11)
Grade 2	1 (5)	
Nausea		
Grade 1	3 (15)	
Grade 2	1 (5)	
Hematology		
Anemia		
Grade 1	13 (65)	14 (74)
Grade 2	2 (10)	5 (26)
Rectal toxicity		
Grade 1	11 (55)	11 (58)
Urinary toxicity		
Grade 2	18 (90)	14 (74)
Grade 3	2 (10)	5 (26)

No severe AE
No cardiac event

Hirano et al. Int Urol Nephrol 42; 81-88, 2010

- **Combination therapy of neoadjuvant ADT + EMP and concomitant with RT (70Gy) sustains freedom from PSA relapse in intermediate- to high-risk prostate cancer in the interim period.**
- **However, it is insufficient in preventing distant metastasis and cancer-specific mortality at the long follow-up duration.**

- **Additional interventions**
  - Dose escalation (current standard dose of 76-78 Gy)
  - Adjuvant ADT
    - Short duration (4-6 ms) for intermediate risk
    - Long duration (2-3 ys) for high risk
- **Need a study involving a large volume of patients**

Summary

- **Intermediate-risk**
  - EBRT (IMRT) with short-term ADT is a standard radiotherapy.
- **High-risk**
  - EBRT (IMRT) with long-term ADT is a standard radiotherapy.
  - The use of a combined modality approach, consisting of dose-escalation, irradiation to the pelvic lymph nodes in especially locally advanced cases may be efficient.
  - Studies on combined with chemotherapy using docetaxel plus EMP and ADT are under way.
  - Neoadjuvant with EMP plus ADT and concurrent with current standard dose EBRT plus adjuvant long-term ADT may be more efficient for preventing cancer relapse.


Thank you very much