

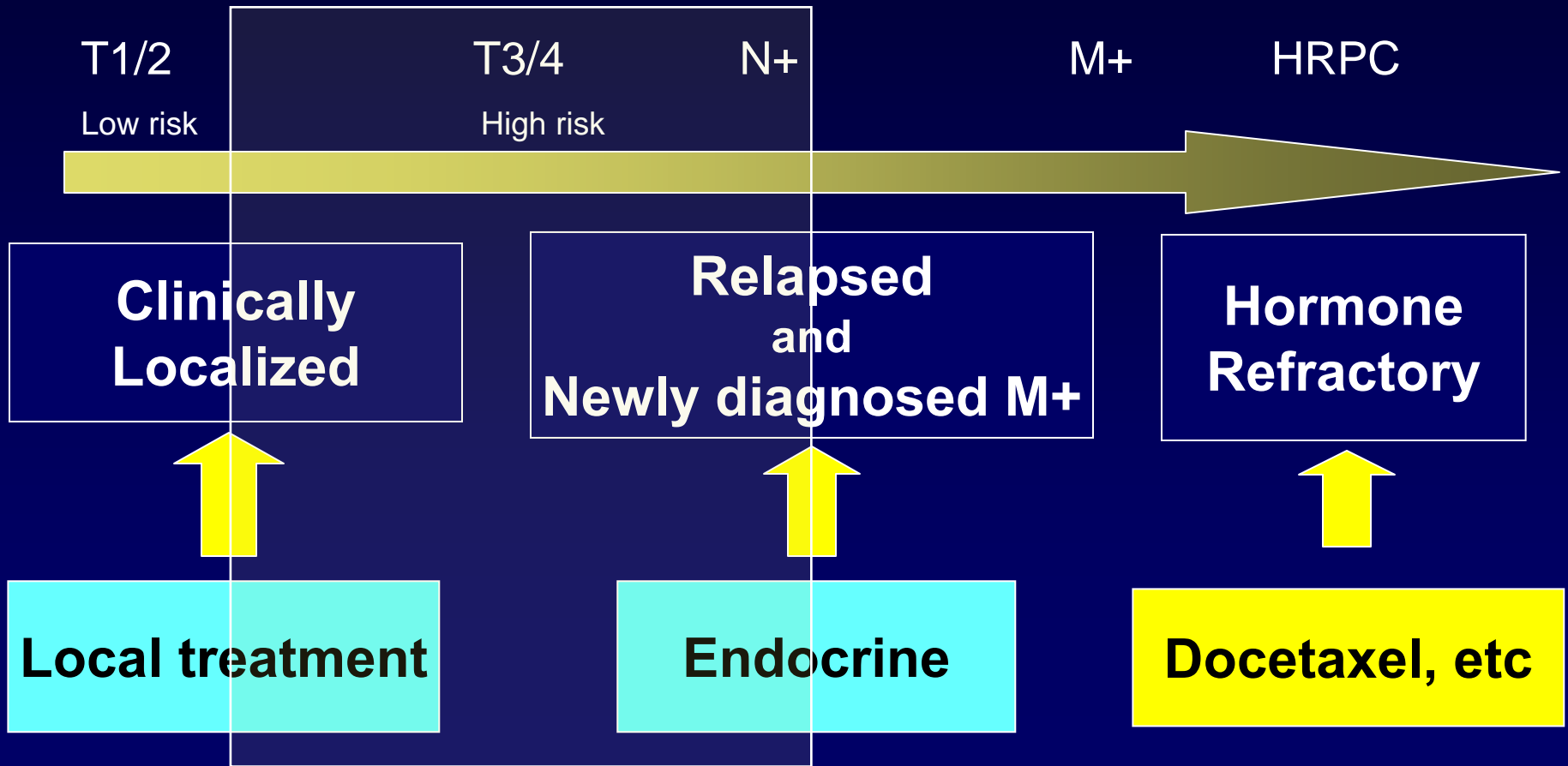
Optimising the Role of Irradiation in High Risk Prostate Cancer

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Introduction

- Overview of problem
- Radiotherapy dose issues
- Radiotherapy volumes
- Integration with hormone therapy
- Conclusions

Prostate Cancer Treatment Paradigms



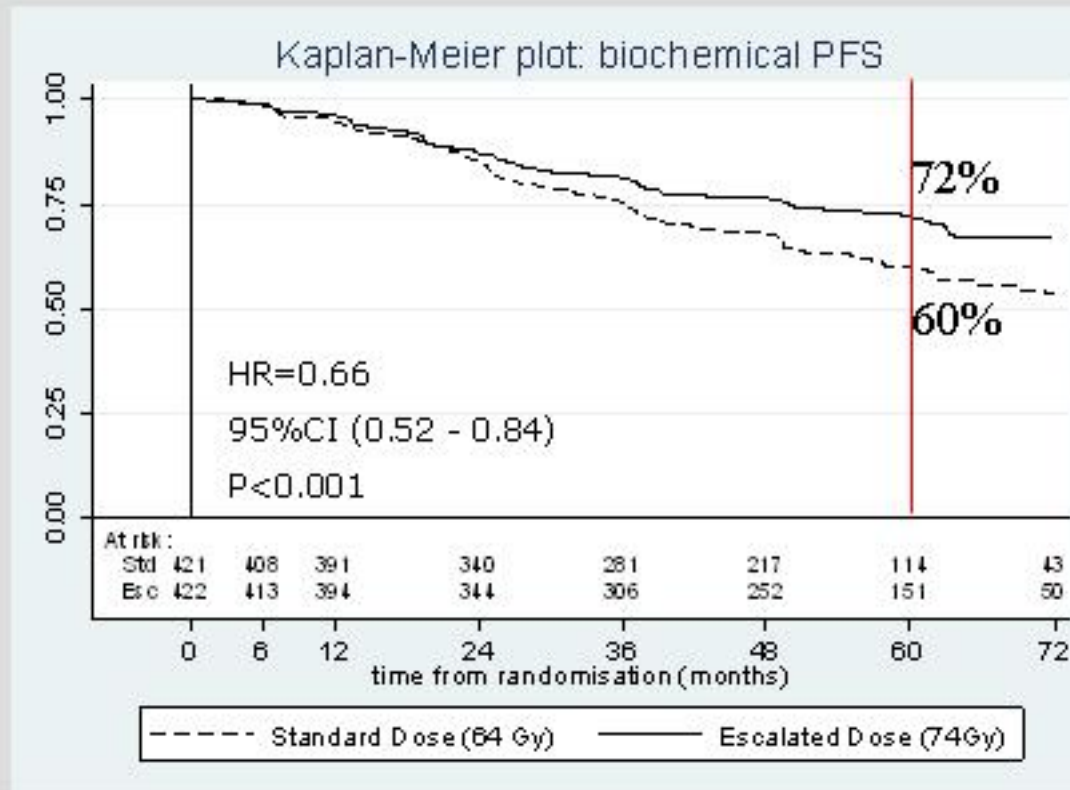
Treatment of Localised Disease - Dose Effects

RT Dose – 64 vs 74 Gy RT01 Trial

Biochemical PFS



Time until first event of PSA 2ng/ml or restart of hormone treatment



Fractionation

- Recent analyses suggest α/β ratio for prostate cancer low
- This predicts that high dose/fraction should be more effective
- Also increases risk of late effects

CHIPP Trial

T1B – T3A N0 M0
Estimated Risk of SV Involvement $\leq 30\%$
PSA ≤ 30 ng/ml

Randomise

Group 1

74Gy / 37F
7.5 weeks

(Standard)

Group 2

60Gy / 20F
4.0 weeks

(Hypofractionation)

Group 3

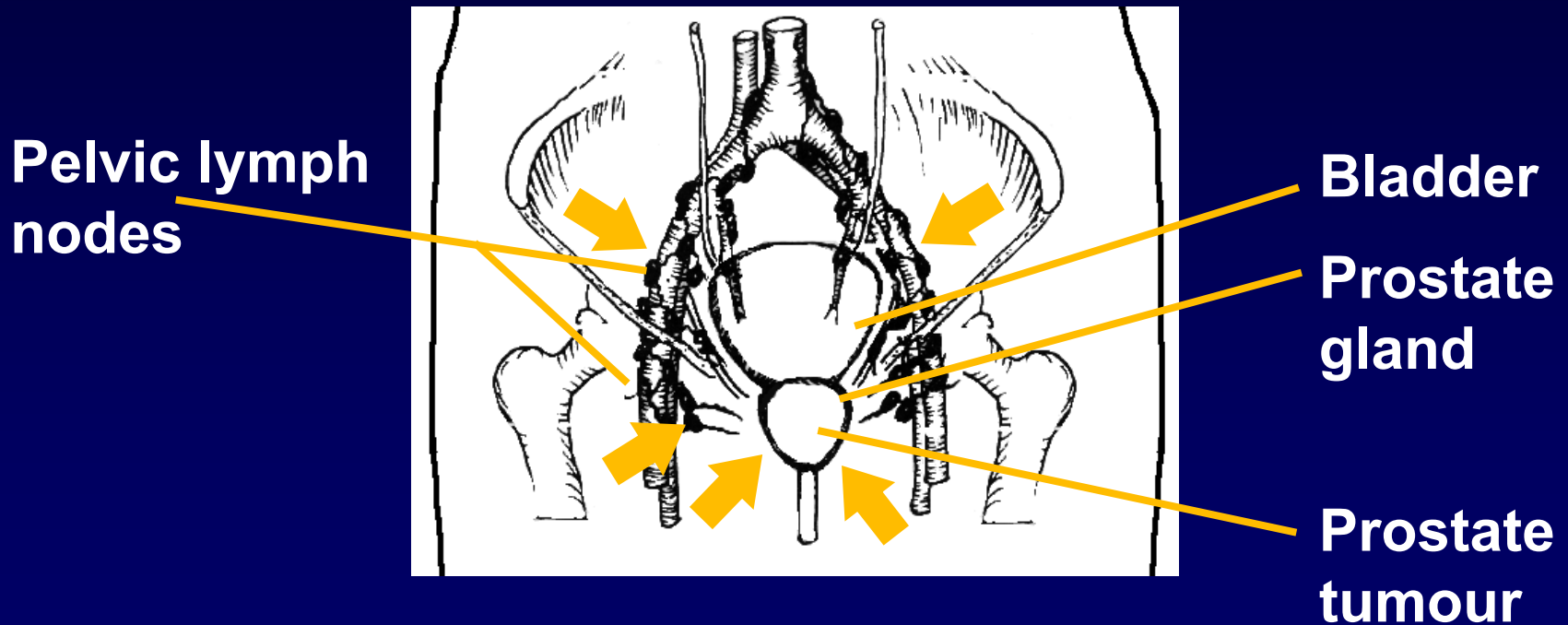
57Gy / 19F
3.8 weeks

(Hypofractionation)

CHIPP Pilot

- Hypofractionation safe
- Late toxicity acceptable
- Phase 3 should proceed

Radiotherapy Volume – Prostate Only or Include the Nodes?



ECOG 7887 Trial: Study Design

Radical prostatectomy
+ lymph node dissection
T1/T2, N+ (n=98)

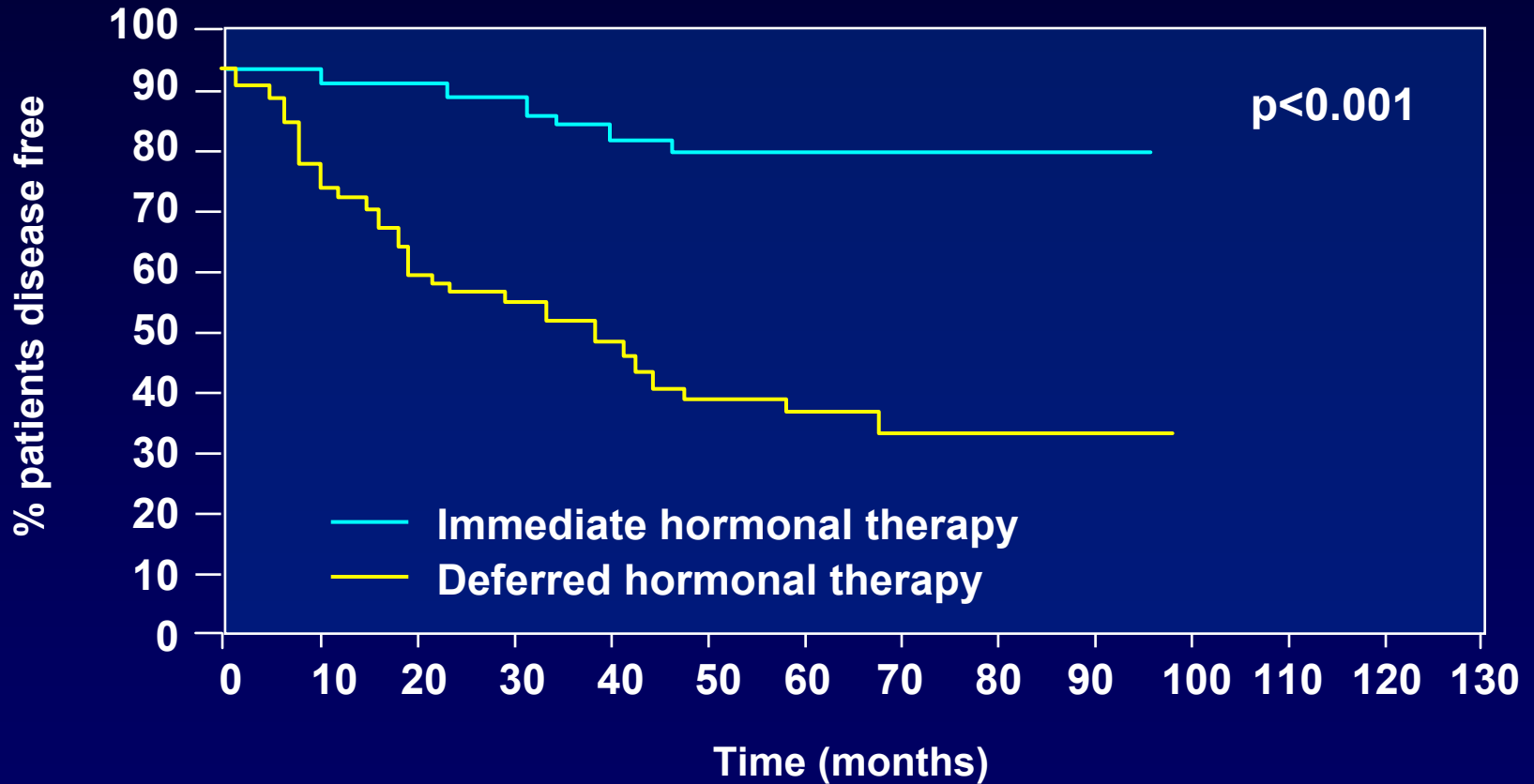
Randomised

Immediate hormonal
therapy (70% goserelin,
30% bilateral orchiectomy)
(n=47)

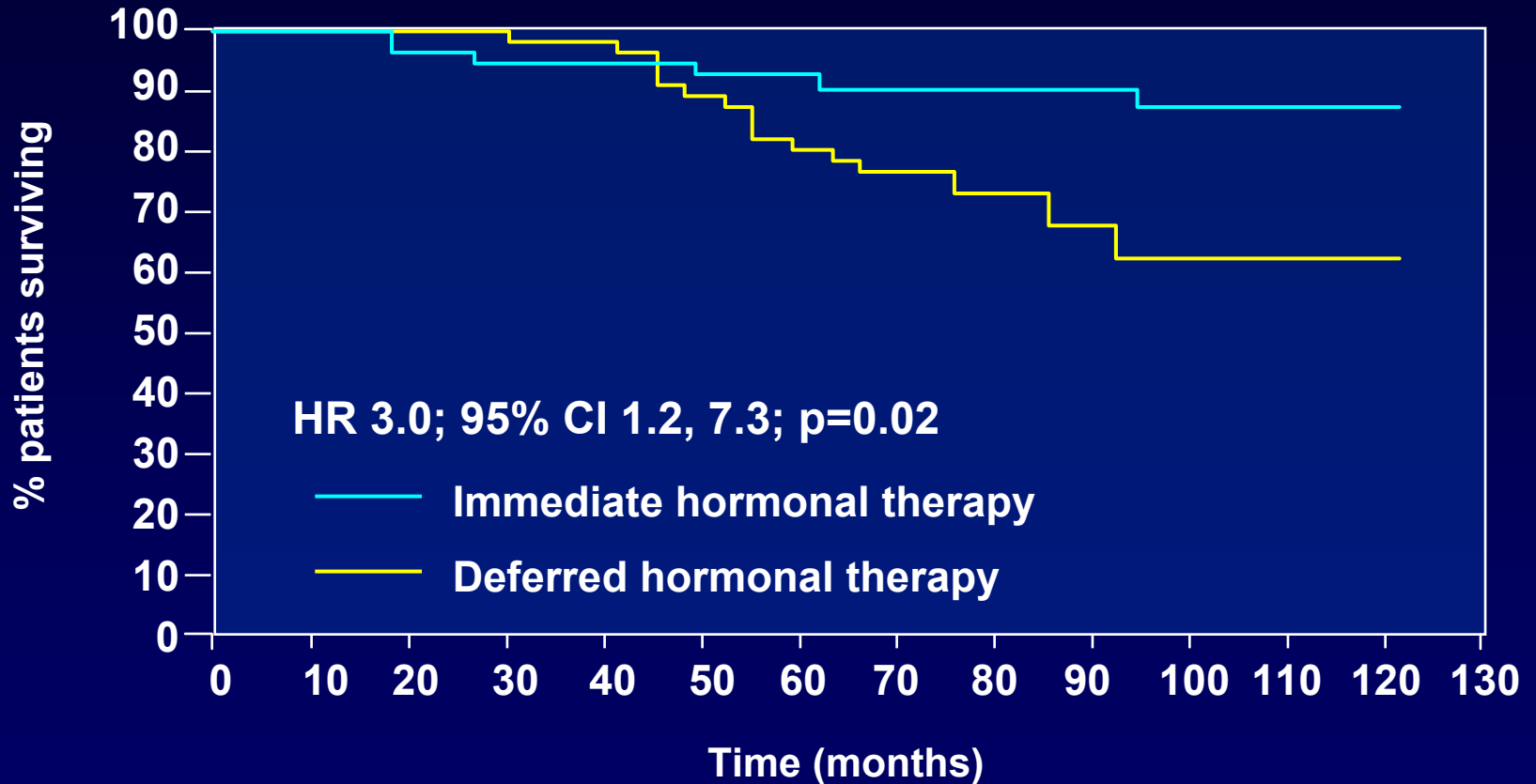
Observation until
progression
(n=51)

Survival status
7.2 year follow up

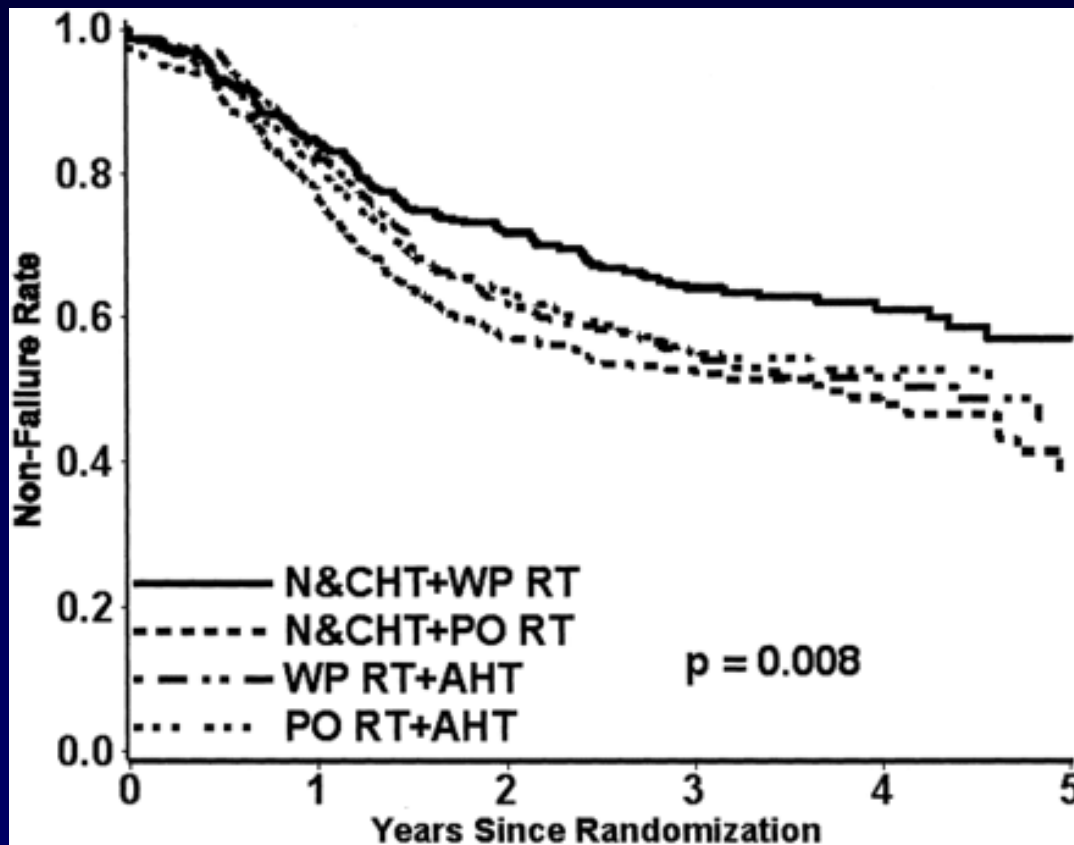
ECOG: Disease-Free Survival



ECOG: Overall Survival



High Risk Patients: Whole Pelvis vs Prostate only RT



GETUG-01

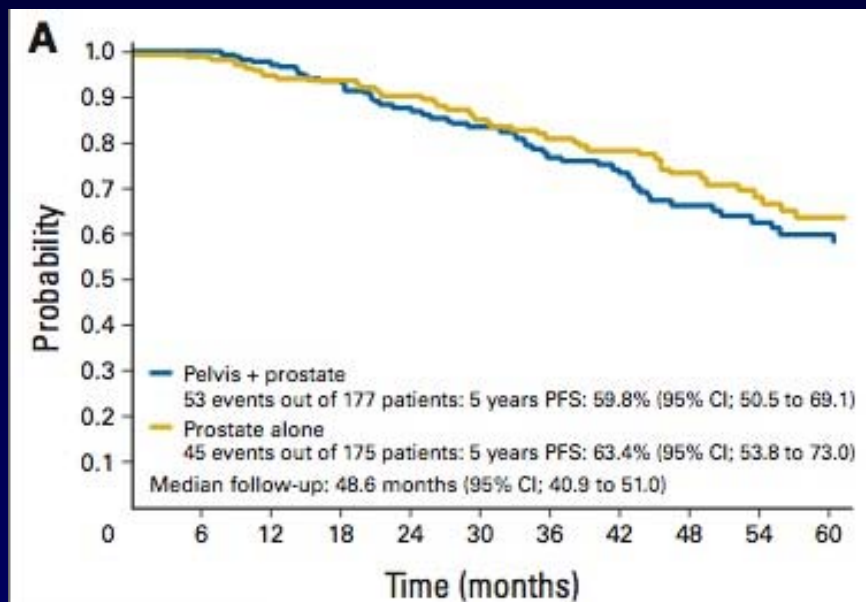
- **T1-3, N0 or Nx**
- **No Gleason or PSA limits**
- **Randomised to RT to prostate only or prostate + nodes**
- **Powered to detect improvement from 60-75% in PFS at 5 years**
- **N=446**

GETUG-01 patient characteristics

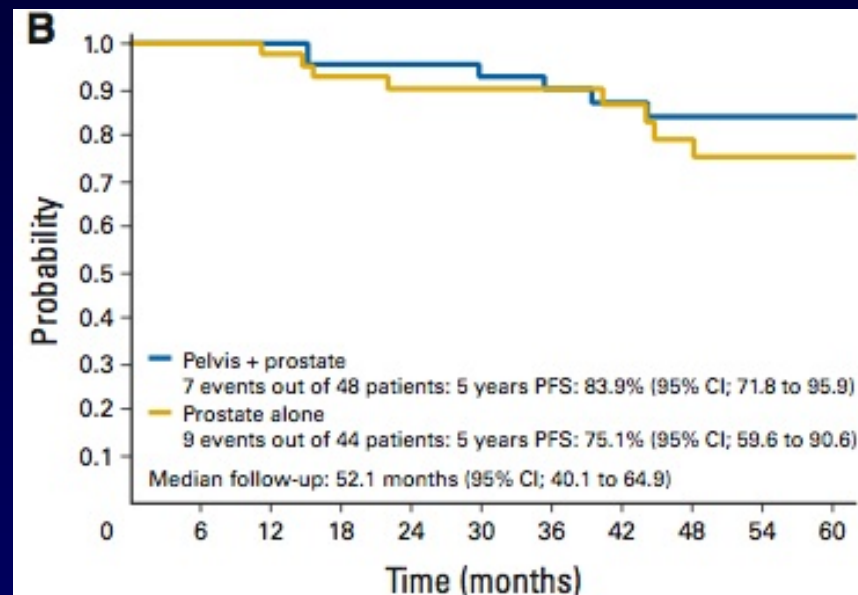
Characteristic	Pelvis + Prostate (n = 225)	Prostate Only (n = 221)	P
Prognostic group, % of patients			.727
Low risk	21.3	19.9	
High risk	78.7	80.1	
Age at diagnosis, years			.812
Mean	68.8	68.9	
SD	5.0	4.9	
Median	69.8	69.9	
Range	52.6-75.6	49.2-75.8	
Tumor stage, % of patients			.648
T1	25.1	21.9	
T2	50.7	50.7	
T3	24.2	27.4	
PSA, $\mu\text{g/L}$.359
Mean	16.3	15.0	
SD	16.5	14.7	
Median	12.0	11.0	
Range	0.2-144.0	1.3-150.0	
Gleason score, % of patients			.432
≤ 6	50.9	48.6	
7	36.6	41.7	
8-10	12.5	9.6	

Pommier et al, Is there a role for pelvic irradiation in localized prostate adenocarcinoma? Preliminary results of GETUG-01. *JCO* 2007 Dec 1;25(34):5366-73.

GETUG-01 PFS results



High risk



Low risk

Pommier et al, Is there a role for pelvic irradiation in localized prostate adenocarcinoma?
Preliminary results of GETUG-01. *JCO* 2007 Dec 1;25(34):5366-73.

Integrating Hormone Therapy

RTOG 8610

(T1-4, N0, M0)
(n=471)

Randomised

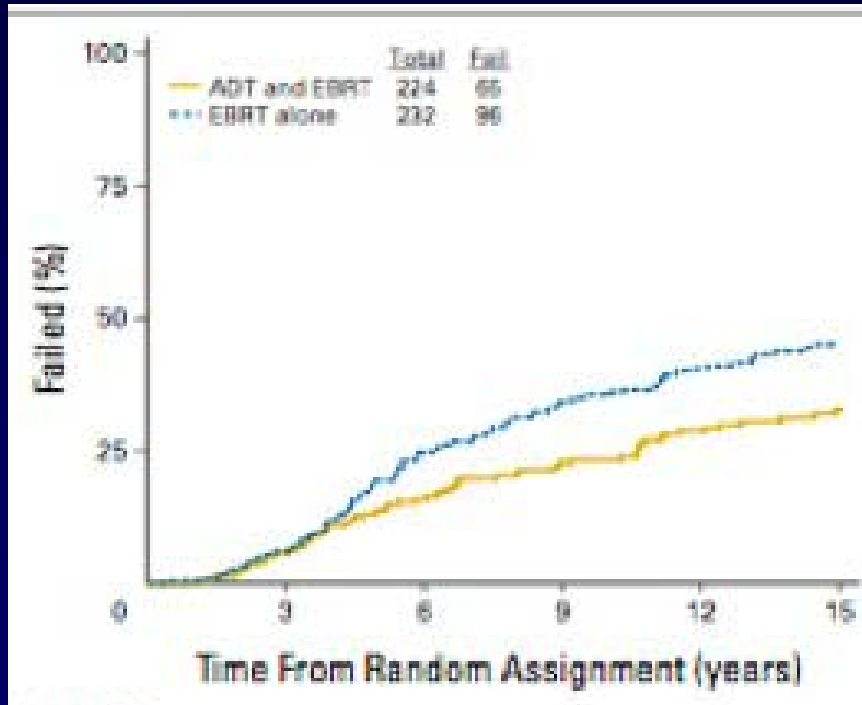
Radiotherapy +
goserelin
monthly x4 (n=221)

Radiotherapy alone
(n=232)

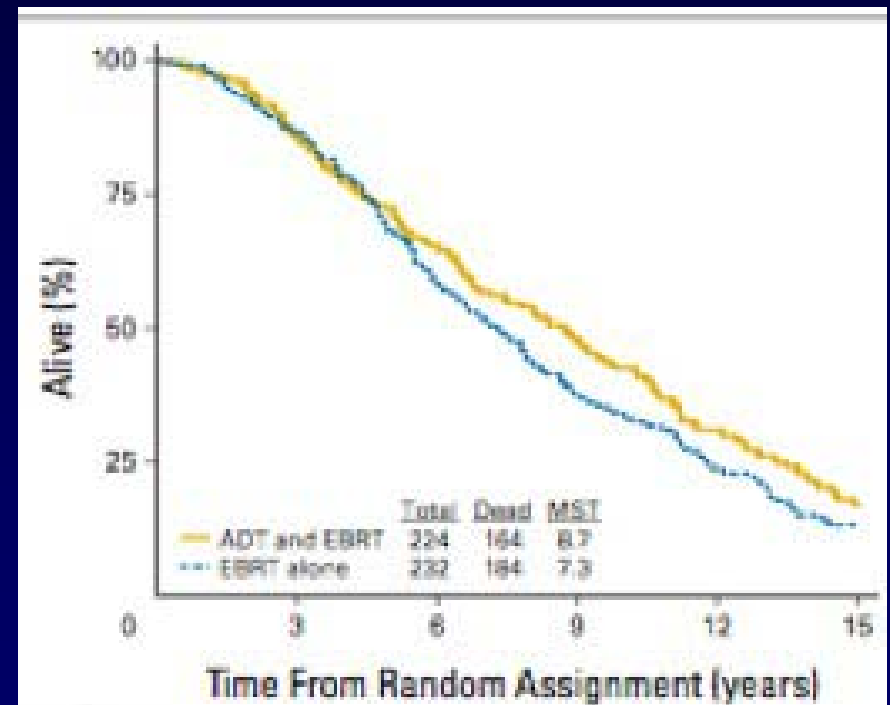
Hormonal therapy
at progression

RTOG 8610 Outcomes

Disease specific survival

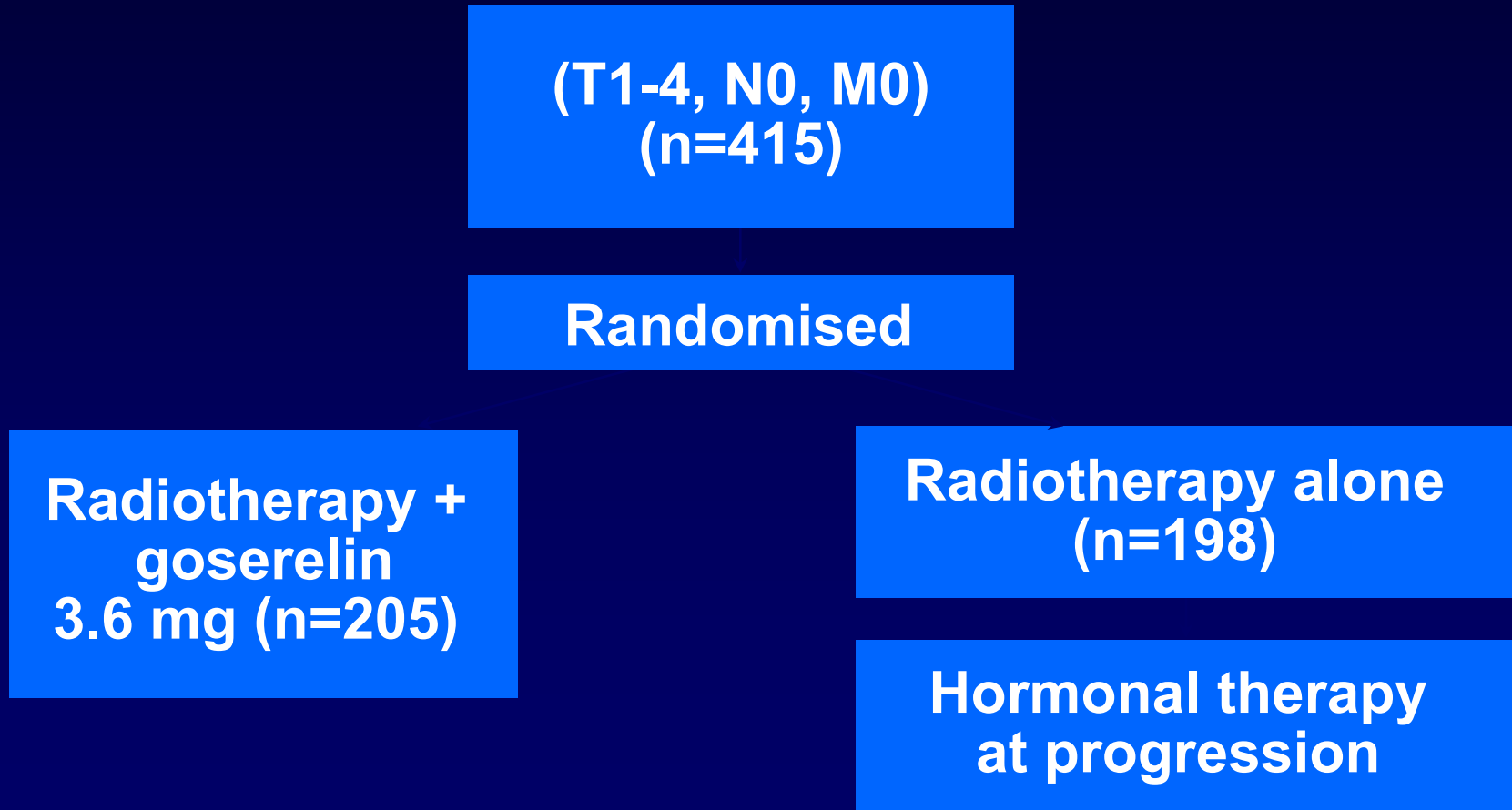


Overall survival



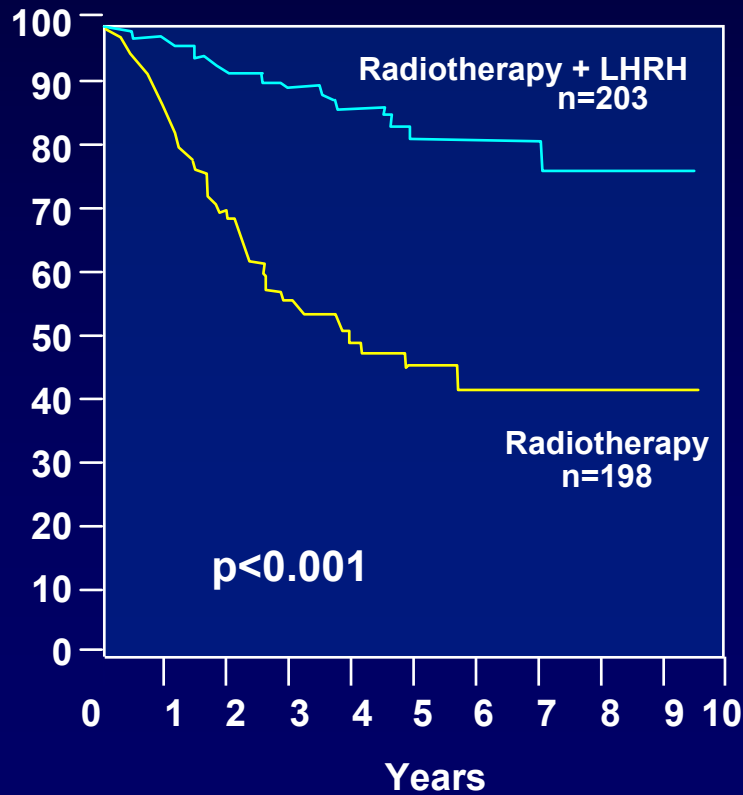
Adjuvant Hormone Therapy

EORTC 22863 Trial: Study Design

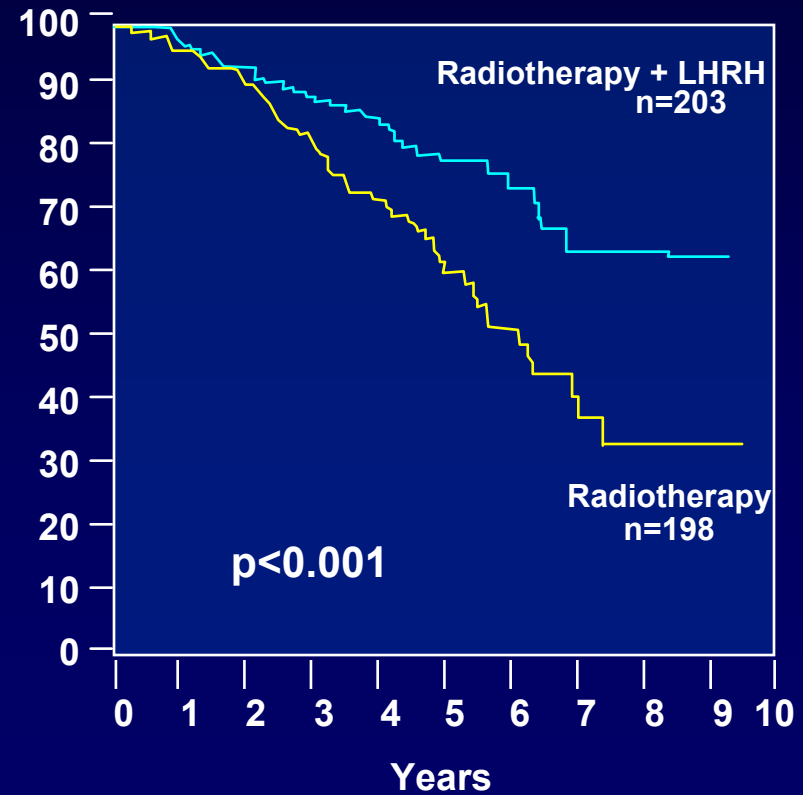


Bolla: EORTC 22863

Disease-free survival



Overall survival



RTOG 85-31 Trial: Study Design

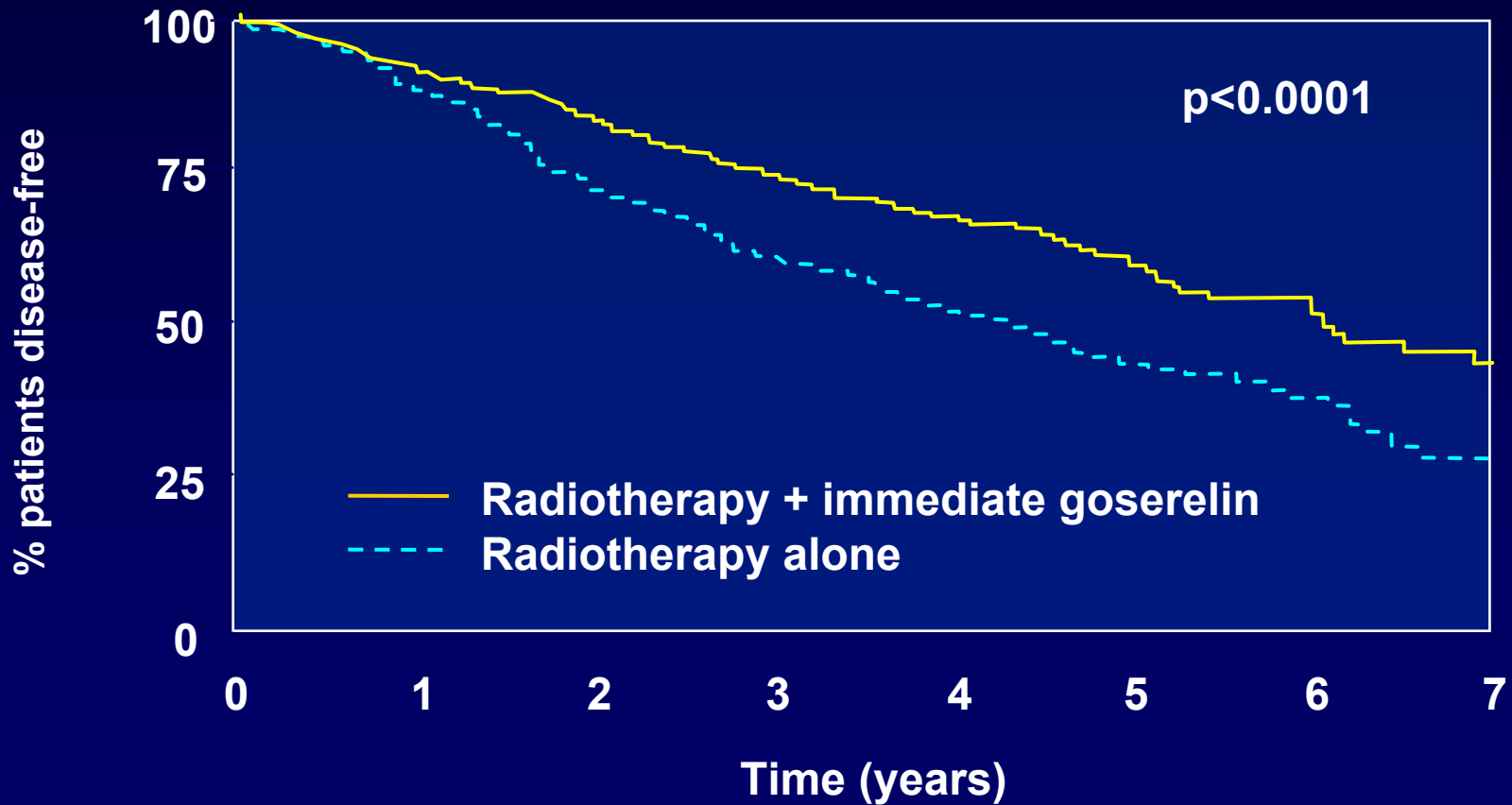
Locally Advanced
(T1-2, N+, T3)
(n=954)

Randomised

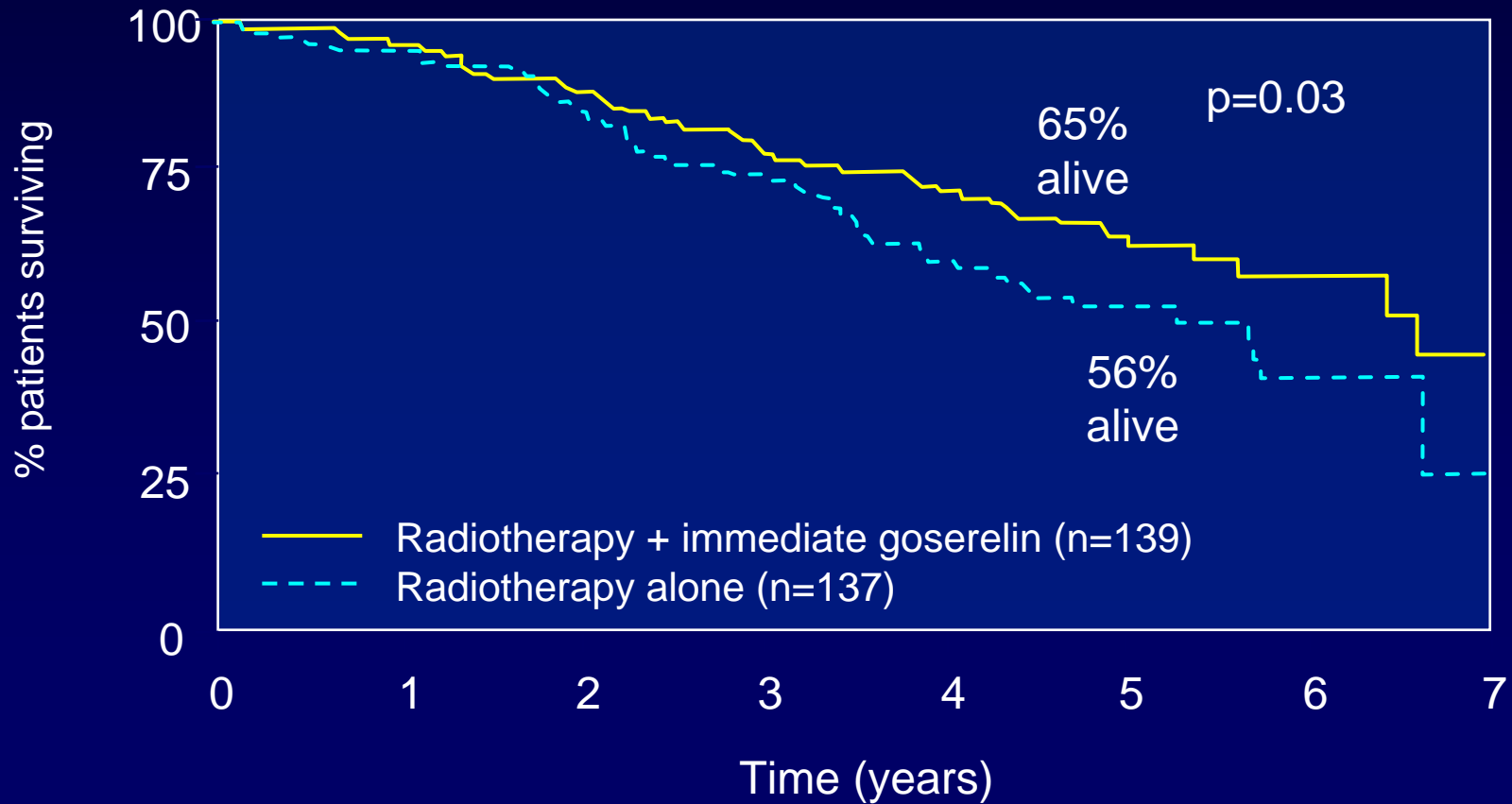
Radiotherapy +
goserelin
3.6 mg (n=477)

Radiotherapy alone
(n=468)

RTOG 85-31: Disease-Free Survival



RTOG 85-31: Overall Survival in Patients With Gleason Score 8-10



RTOG 92-02: Study Design

Locally advanced
prostate cancer (T2c-4)
(n=1554)

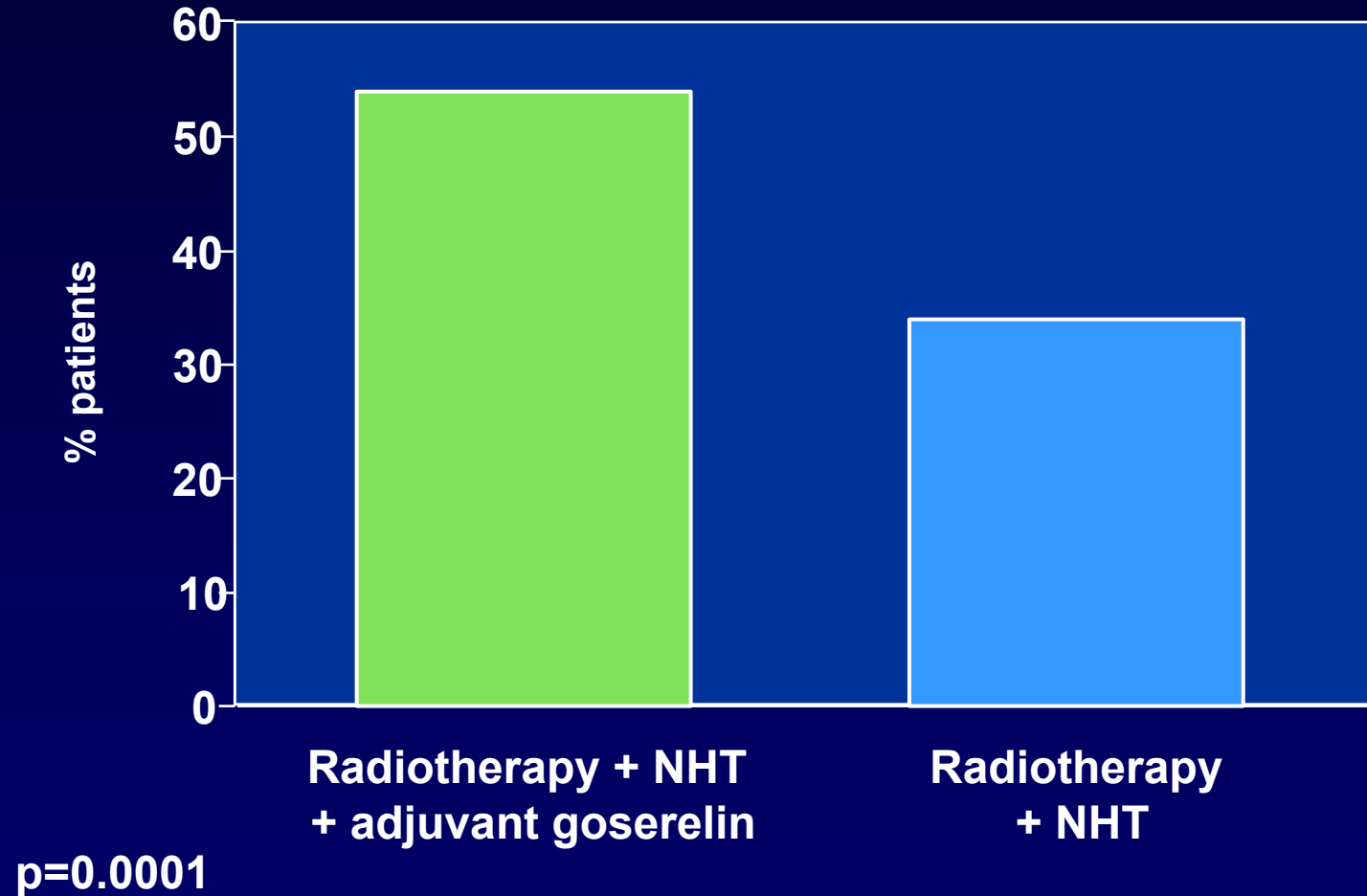
Goserelin + flutamide
2 months before +
2 months during radiotherapy

Randomised

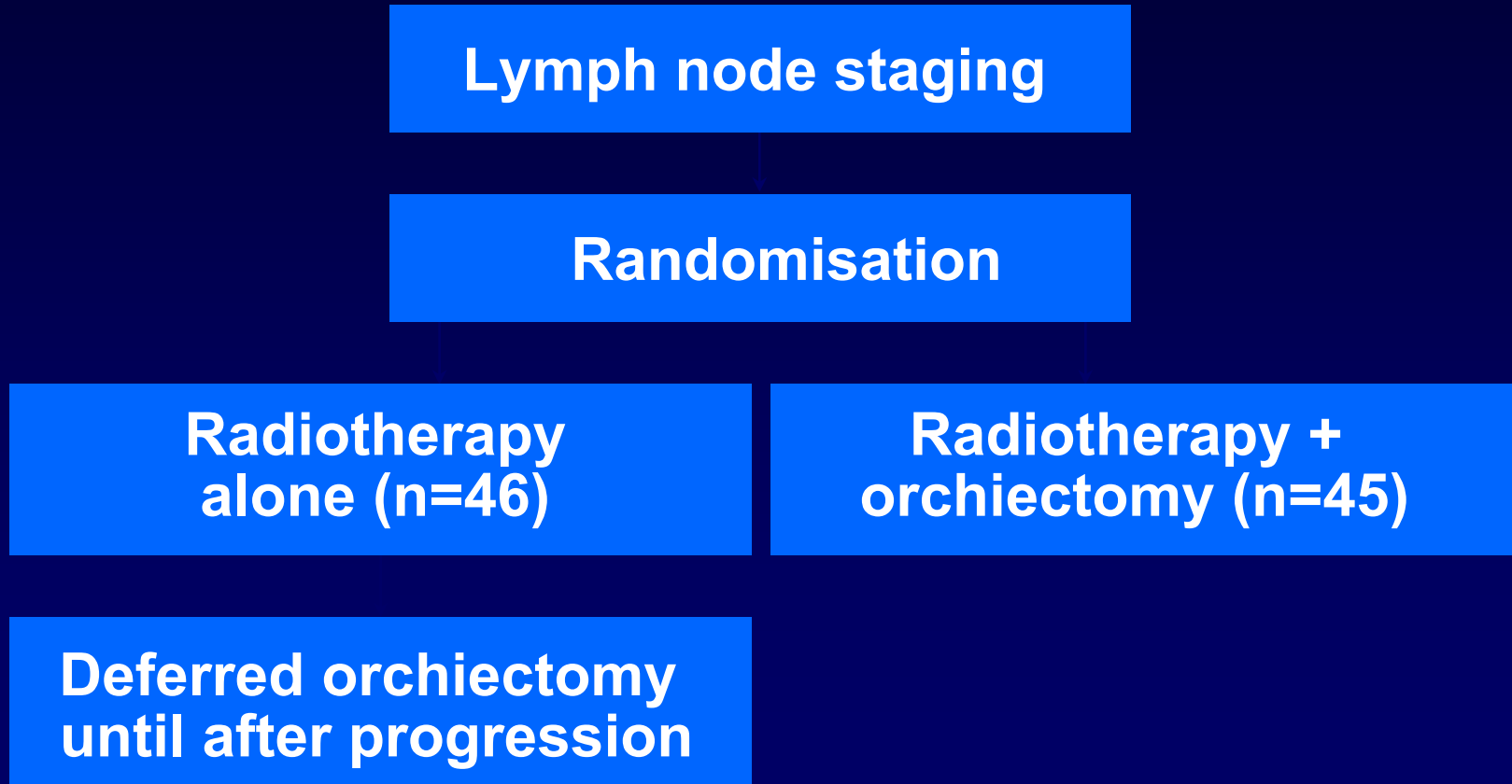
24 months goserelin

No further therapy

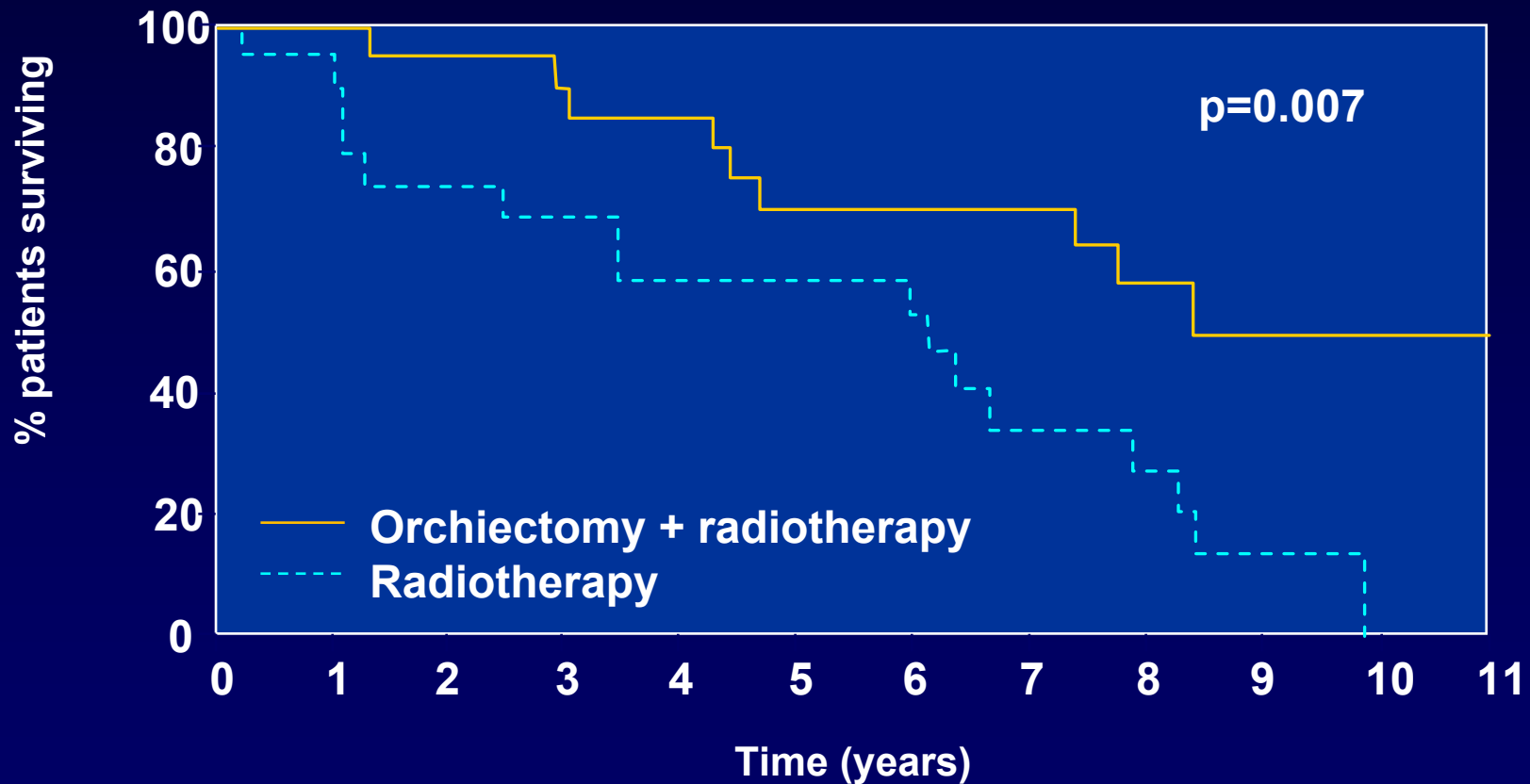
Disease-Free Survival: Median Follow-up 4.8 Years



Granfors et al: Study Design



Granfors et al: Overall Survival Median Follow-up 9.3 Years N+ Patients n=39



Radiotherapy With or Without Orchiectomy

Conclusion:

- **Early androgen deprivation is better than deferred endocrine treatment for patients with pelvic lymph node involvement**

SPCG-7

- Compared neoadjuvant androgen radical RT to nodes plus prostate then oral anti-androgen with hormone therapy alone
- Essentially the “mirror” of EORTC 22863

SPCG-7

Locally advanced
CaP
PSA up to 70
(n=880)

Randomised

Initial androgen ablation
RT 70Gy to Prostate + pelvis
Adjuvant oral anti-androgen

Initial androgen ablation
Switch to
Adjuvant oral anti-androgen

Initial results with 10 year follow up
reported ASTRO 2008

SPCG-7 Results

- 79 cancer deaths HT vs. 27 in RT arm, RR 0.44, p=0.00003
- Overall survival 8.5% increased RR 0.68 p=0.004
- PSA relapse 285 (65%) patients HT arm vs 77 (17.5%) RT arm RR 0.16, p=0.00001
- Moderate to severe urinary leakage (6 vs. 3%), dysuria (4 vs. 2%) more common in RT arm
- Erectile dysfunction worse in RT arm, 85 vs. 72% p<0.001

Combinations With Other Systemic Therapies

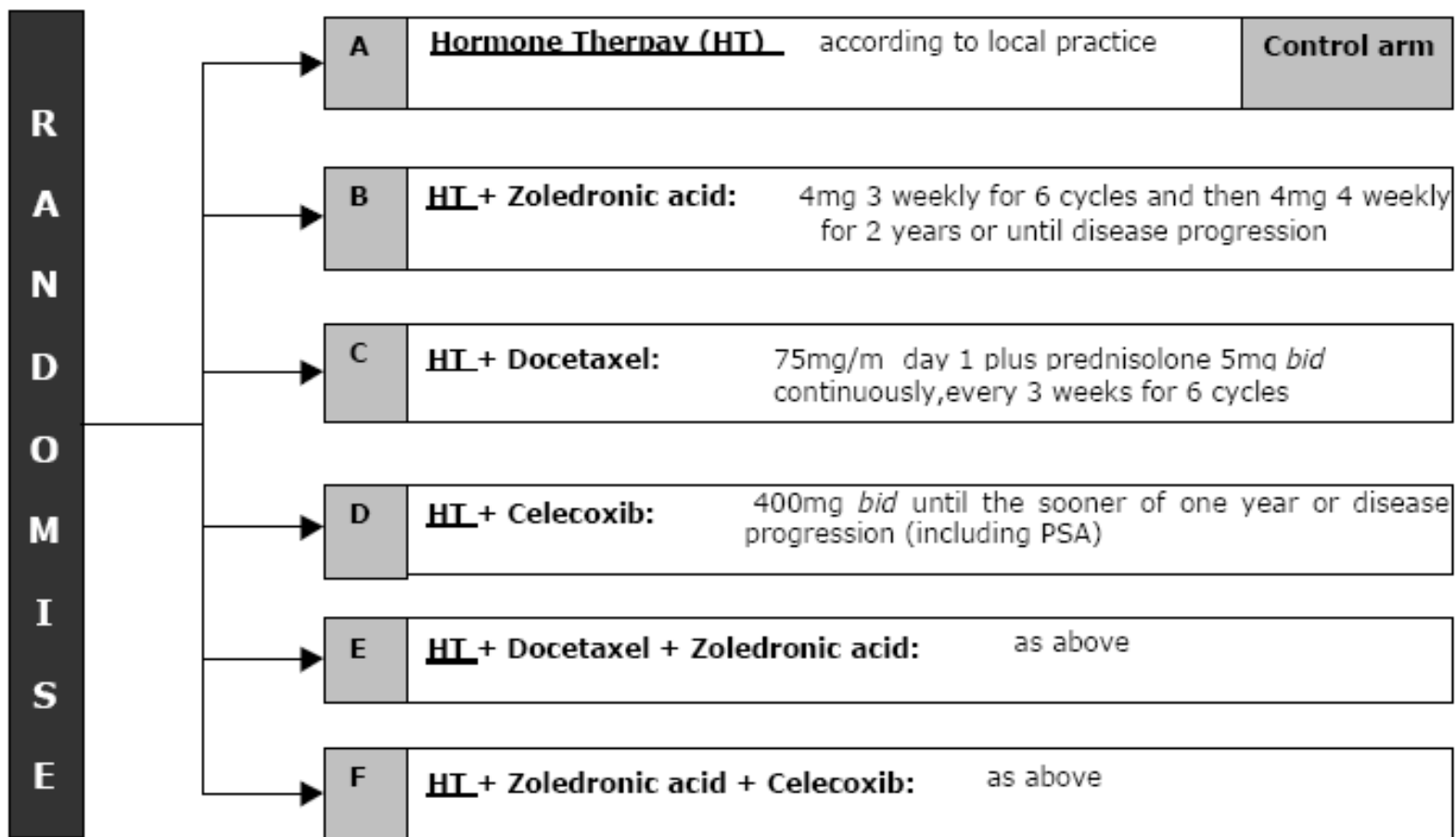


STAMPEDE

Systemic **T**herapy in
Advancing or **M**etastatic
Prostate cancer: **E**valuation
of **D**rug **E**fficacy

www.stampedetrial.org

Stampede Trial Design

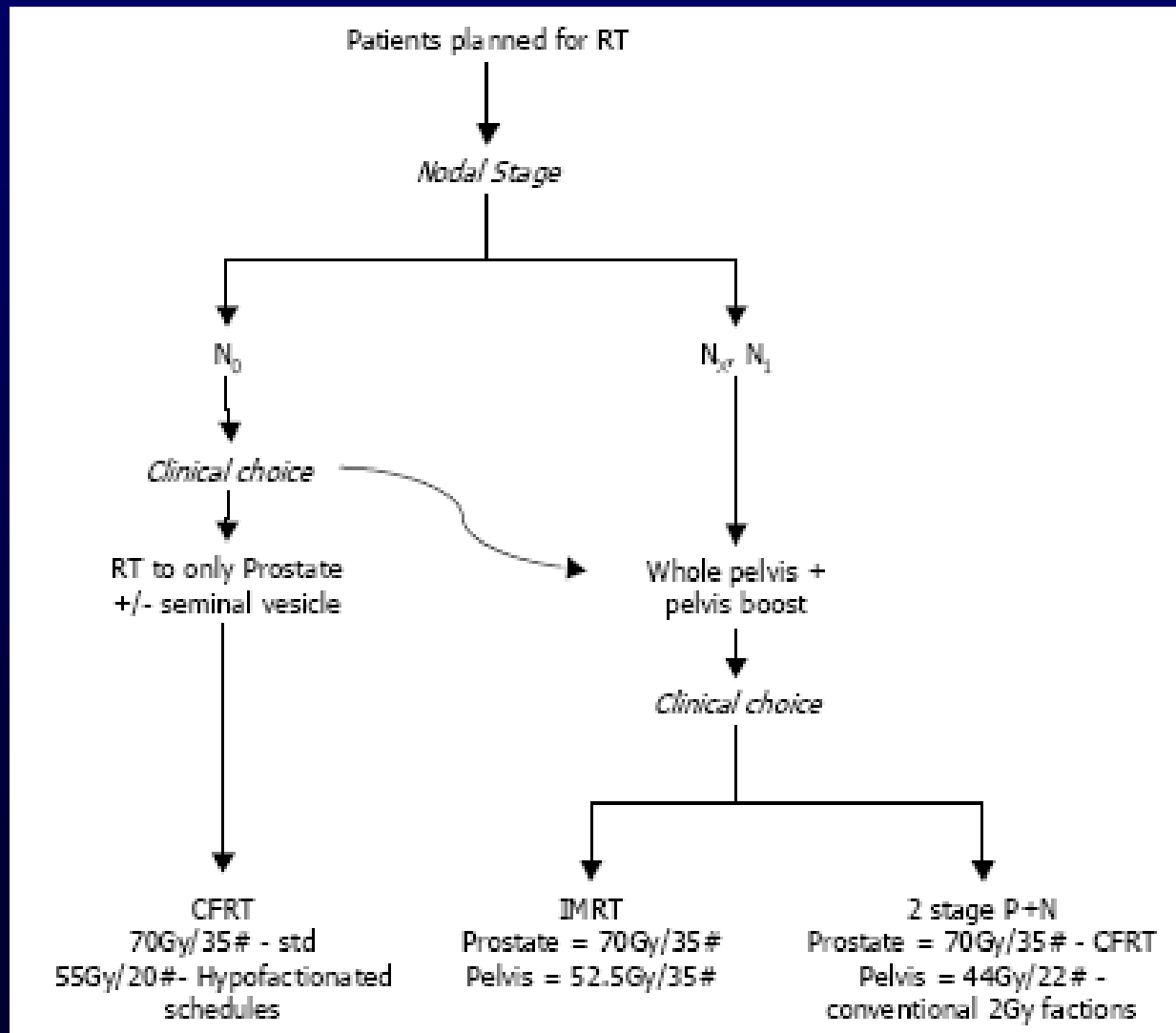


HT= Hormone Therapy as in Arm A

Trial Design Stages and Outcome Measures

Stage	Outcome Measures	
	Primary	Secondary
Pilot	Safety	Feasibility
Efficacy I-III	Failure-free survival	Overall survival Toxicity Skeletal-related events
Efficacy IV	Overall survival	Failure-free survival Toxicity Skeletal-related events Quality of life

Radiotherapy



Patient Characteristics

Age:	64yr mean & 64yr median 45 – 81 range
Disease:	90% newly diagnosed
Metastases:	62%
PSA:	57ng/ml median 123ng/ml mean
RT planned:	23%

Current Recruitment Status

First patient

- 17th October 2005

Accrual targets

- Pilot Phase 210 patients
- 1st efficacy analysis 1000 patients
- Overall target 3300 patients

Current accrual

- 709 patients Sept 2008
- 23% receiving RT

Conclusion

- **Optimal treatment requires combination of radiotherapy and hormone therapy**
- **Optimal treatment volumes undefined**
- **Even with high-risk disease, patients can be cured so hormone therapy should be limited duration**
- **Future combinations with non-hormone therapy to be defined**