



# Greater Than 6 Months of Androgen Deprivation Therapy Does Not Improve Overall Survival for High-risk Prostate Cancer Patients Treated With Radiotherapy or Prostatectomy

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## Introduction

- Two large randomized trials (RTOG 85-31, EORTC 22863) have demonstrated an overall survival benefit for the addition of long-term (at least 2 years) androgen deprivation therapy (ADT) to external beam radiation in the definitive management of prostate cancer. Another trial failed to show an overall survival benefit to the use of long-term androgen deprivation compared to short term use (RTOG 92-02).
- Whether these studies apply to our current population of patients is confounded by several factors, notably:
  - Most of the patients in these studies had locally advanced prostate cancer.
  - These studies were completed in the pre-PSA era.
  - The doses of radiation used are significantly lower than that used today.
  - The criteria used to define Gleason score has undergone a dramatic shift, resulting in a so-called “Will Rogers” effect.
  - Since most patients are no longer locally advanced at diagnosis, patients are now treated based on categorization into risk groups based on Gleason score, initial PSA, and AJCC stage.
- A recent trial by D’Amico, *et al*, completed in the PSA-era, and comprised of “modern” patients, demonstrated an OS benefit to the use of short-term (6 months) androgen deprivation in high-risk disease.
- Long-term androgen deprivation carries with it a host of potential side effects, including decreased libido, impotence, hot flashes, osteoporosis, gynecomastia, anemia, loss of muscle mass, fatigue, depression, decreased mental acuity, and alterations in cholesterol levels.
- Whether long-term androgen deprivation is still important for overall survival in modern era patients with high-risk features treated with surgery or current radiotherapy remains in question.

## Purpose

To analyze the effect of the duration of androgen deprivation (AD) in the definitive treatment of high-risk prostate cancer.

## Materials/Methods

579 patients with high-risk prostate cancer were treated definitively at the Cleveland Clinic from 1998 to 2003.

- External beam radiation (RT, n=390)
- Radical prostatectomy (RP, n=165)
- Permanent prostate implant (PI, n=24)

## High-risk disease definition

- Initial PSA (iPSA) > 20
- Gleason score (GS) 8-10
- Clinical stage T3
- or iPSA 10-20 and GS 7

## Study Endpoints

Biochemical failure (bF)

- ASTRO consensus definition for RT and PI patients.
- Two consecutive PSA's  $>0.2\text{ng/ml}$  for RP patients.

Clinical failure (cF)

- Detection of biopsy proven local recurrence, or evidence of definite metastases to bone, lymph nodes, or elsewhere.

Overall survival (OS)

## Statistics

- Cox proportional hazards regression was used to determine what factors, including iPSA, GS, stage, AD, age, race, income, BMI, and smoking history correlated with bF, cF, and OS.

## Table 1 – Patient characteristics

	All	no AD 26.4%	1-6 mths 60.6%	>6 mths 12.8%	p-value
<b>Treatment</b>					<b>&lt;0.0001</b>
PI	4.1%	5.2%	4.0%	2.7%	
RP	28.5%	75.2%	10.8%	14.9%	
RT	67.4%	19.6%	85.2%	82.4%	
<b>Age (yrs)</b>					<b>&lt;0.0001</b>
median	67	63	68	68.5	
<b>iPSA (ng/ml)</b>					<b>&lt;0.0001</b>
median	15.5	13.5	16.4	22	
0-4	2.1%	2.0%	2.3%	1.4%	
4.1-10	18.5%	15.7%	19.7%	17.6%	
10.1-20	41.3%	58.2%	37.3%	25.7%	
>20	37.8%	23.5%	12.3%	54.1%	
<b>bx GS</b>					<b>0.0060</b>
<6	12.8%	13.7%	12.3%	13.5%	
7	51.6%	59.5%	51.9%	35.1%	
>8	35.6%	26.8%	35.9%	51.4%	
<b>Clinical Stage</b>					<b>&lt;0.0001</b>
T1T2A	62.3%	75.8%	58.4%	52.7%	
T2BC	23.0%	19.6%	24.8%	21.6%	
T3	14.7%	4.6%	16.8%	25.7%	

## Table 1 – Patient characteristics (Cont)

	All	no AD	1-6 mths	>6 mths	p-value
		26.4%	60.6%	12.8%	
<b>Race</b>					<b>0.1435</b>
B	23.1%	18.3%	25.9%	20.3%	
W	76.9%	81.7%	74.1%	79.7%	
<b>Income (\$)</b>					<b>0.6393</b>
median	41,943	44,300	41,311	42,674	
<b>Ever Smoked</b>					<b>0.1526</b>
N	37.8%	36.6%	39.9%	31.1%	
Y	52.7%	55.6%	49.0%	63.5%	
<b>Smoking Pack Years</b>					<b>0.9210</b>
median	7	10	5	7.5	
<b>Body Mass Index (Kg/M<sup>2</sup>)</b>					<b>0.0022</b>
median	28.1	27.4	28.2	29.1	

## Results

- Median follow up 60 months (range: 24-114).
- Median age for all patients was 67 years (range: 41-85).
- AD was given to 426 (73.6%) patients:
  - 82.6% 1-6 months (median: 6 months)
  - 17.4% >6 months (median: 15 months)

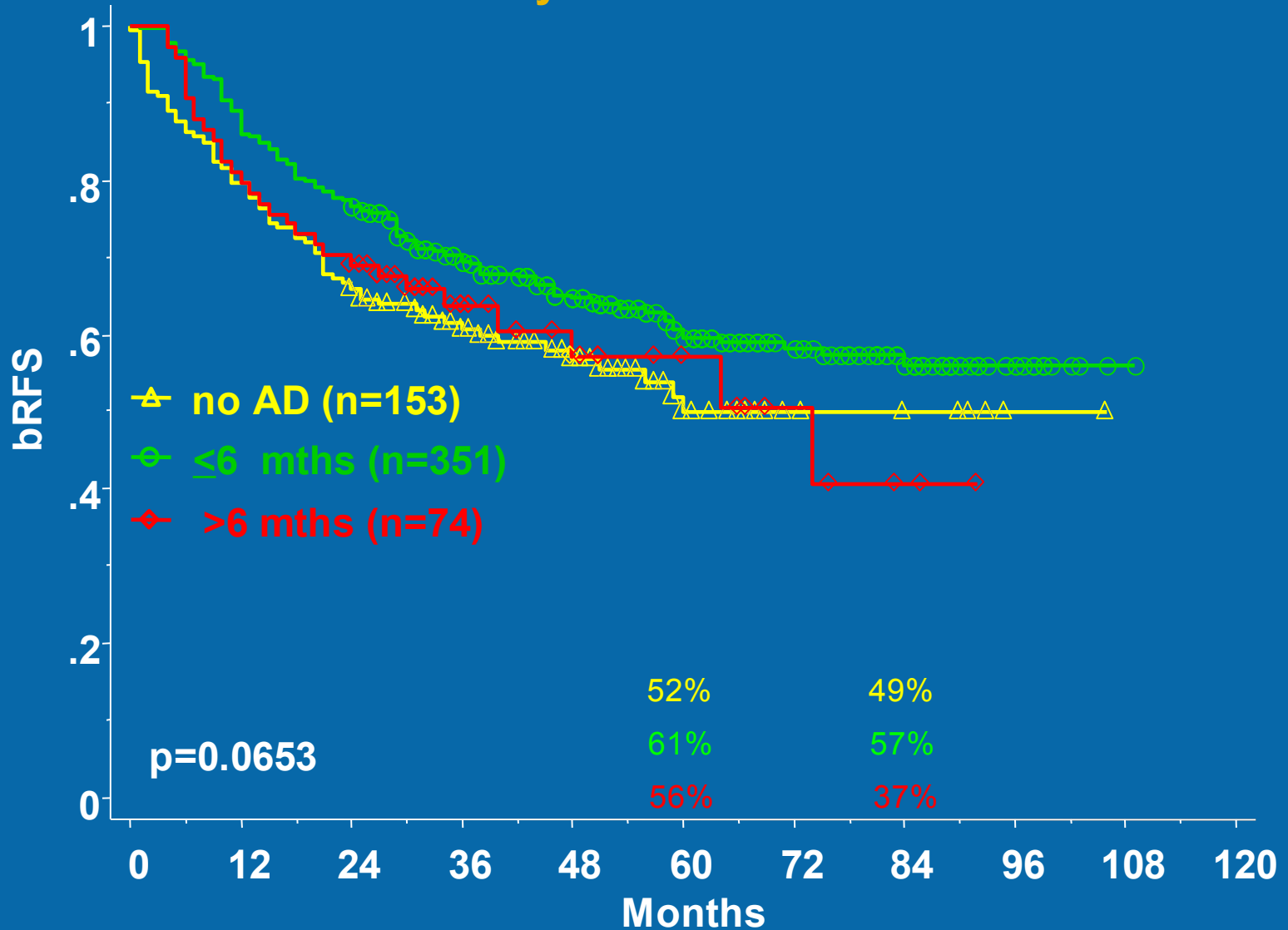
## Univariate analysis for Overall Survival

	p-value**	RR	95% CI
Age	0.0861	1.029	0.996- 1.063
iPSA (cont.)	0.6371	0.996	0.982- 1.011
bx GS	<b>0.0157</b>		
7 vs <6	0.1278	2.238	0.973- 6.310
>8 vs<6	0.0142	3.648	1.296- 10.270
Clinical Stage	0.1892		
T1T2A vs T3	0.0713	0.582	0.323- 1.048
T2BC vs T3	0.3618	0.739	0.385- 1.417
TX	0.3104		
PI vs RT	0.7925	0.766	0.105- 5.571
RP vs RT	0.1285	0.643	0.364- 1.136
AD (N vs Y)	0.6976	0.898	0.521- 1.546
AD Duration	<b>0.0012</b>		
1-6 mths vs none	0.7331	0.906	0.513- 1.599
>6 mths vs none	0.0058	2.62	1.323- 5.195
Race (B vs W)	0.5867	0.860	0.500- 1.481
Ever Smoked (N vs Y)	0.0809	0.641	0.389- 1.056
Current Smoker (N vs Y)	<b>0.0467</b>	0.586	0.346- 0.992
Smoking Pack Yrs (cont.)	<b>0.0139</b>	1.010	1.002- 1.019
bF (N vs Y)	<b>&lt;0.0001</b>	0.308	0.186- 0.513
Clinical failure (N vs Y)	<b>&lt;0.0001</b>	0.113	0.071- 0.179
Income by Zip Code (cont.)	0.4013	1.000	1.000- 1.000

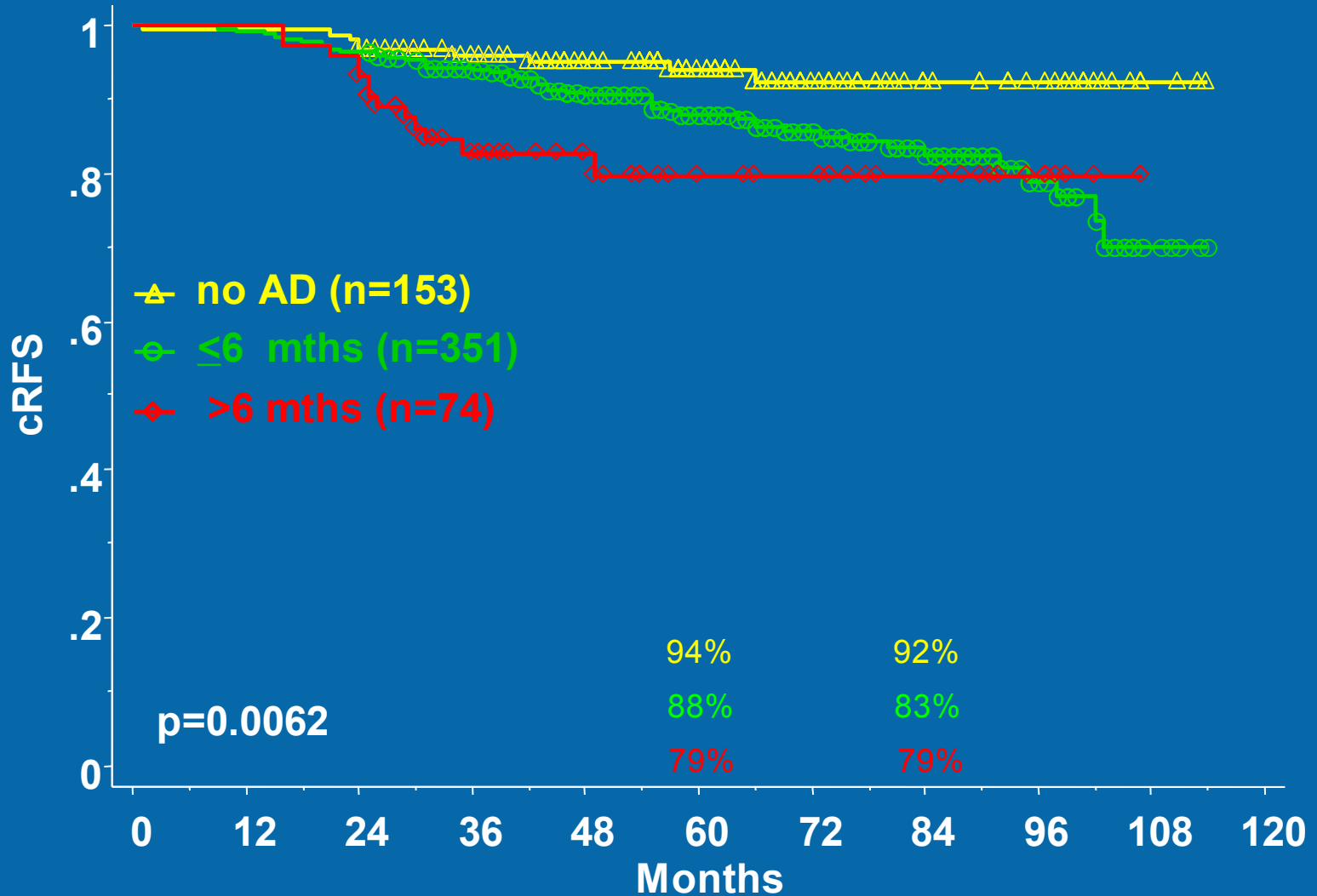
## Univariate analysis

- > 6 months of AD had no statistically significant impact on bF and did not improve cF.
- > 6 months of AD did result in a statistically significant worse OS (p=0.0003).
- Other factors found to result in worse OS:
  - GS  $\geq$  8 (p=0.0424)
  - Active tobacco use (p=0.0467)
  - Increasing number of pack-years smoked (p=0.0139)

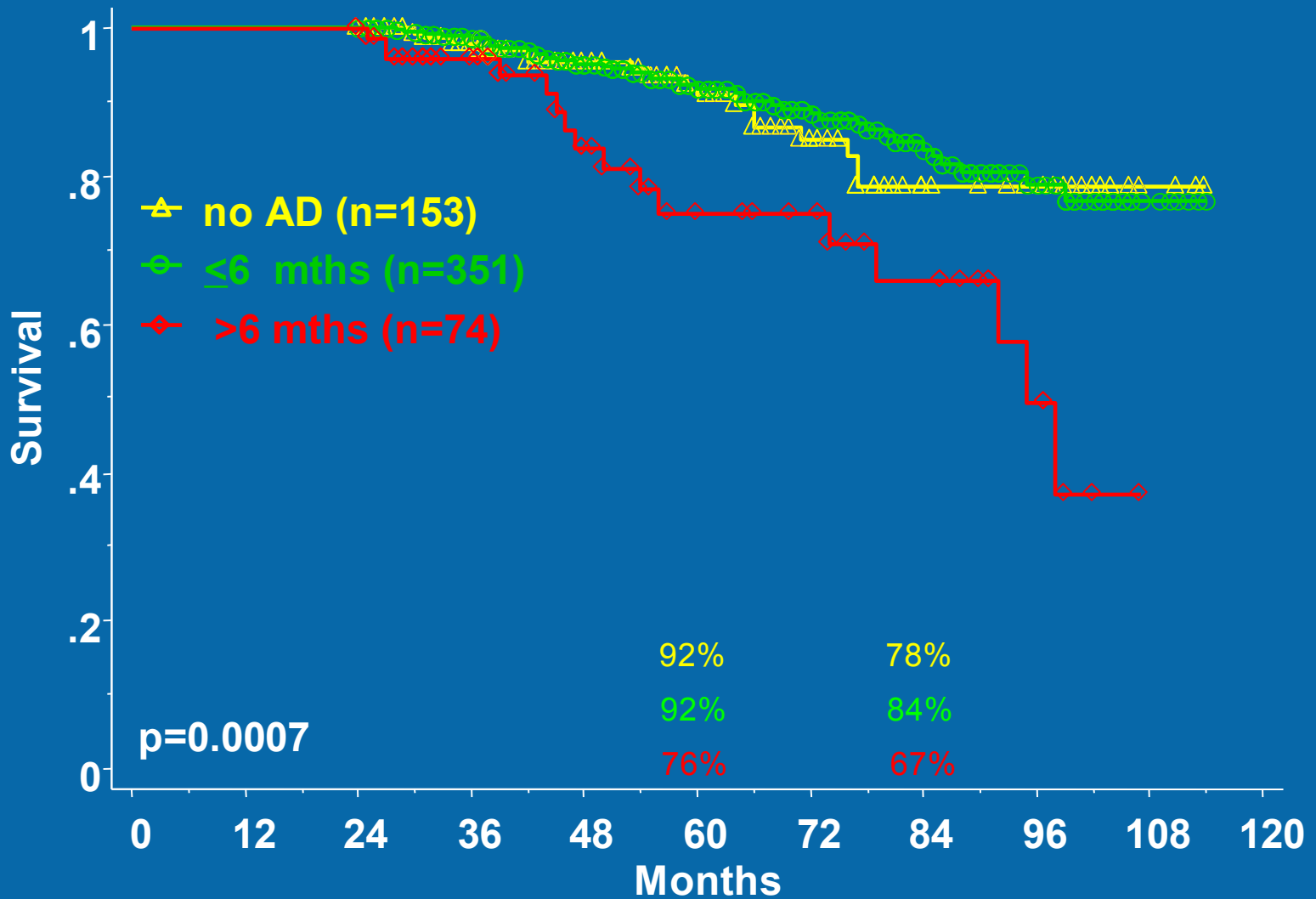
## bRFS by Duration of AD



# Clinical Failure by Duration of AD



# Overall Survival by Duration of AD



## Multivariate analysis for Overall Survival

	p-value	RR	95% CI
<b>AD Duration</b>	<b>0.0056</b>		
1-6 mths vs none	0.5100	0.820	0.455- 1.479
>6 mths vs none	0.0329	2.158	1.064- 4.373
<b>bx GS</b>	<b>0.0101</b>		
7 vs ≤6	0.1234	2.269	0.798- 6.450
≥8 vs ≤6	0.0104	3.887	1.376- 10.975
<b>Pack Yrs (cont.)</b>	<b>0.0161</b>	1.010	1.002- 1.019

## Multivariate analysis:

- >6 months of AD remained an **independent predictor of death** on multivariate analysis. (RR 2.158, p=0.0329)
- Gleason score and increasing number of pack-years smoked also remained independent predictors of death.
- While smoking and use of >6 months of AD both had a detrimental effect on OS, **no synergistic effect** between the two factors was detected.

## Conclusion

- In high-risk patients treated with radiotherapy or prostatectomy, longer duration of androgen deprivation (> 6 months) does not improve biochemical or clinical failure rates, and appears to result in worse overall survival.
- The cause of this lower overall survival is unknown and warrants further investigation.

## Further investigation

### Controlling for co-morbidity

- **Charlson Index**, a validated co-morbidity index.
- Charts are being retrospectively reviewed and coded with the Charlson Index criteria.
- All new patients will have this index data prospectively coded into the database.

### Cause of death information

- CDC National Death Index (NDI), an electronic database of cause of death information derived from death certificates.