April 4th, 2017

Prostate Cancer

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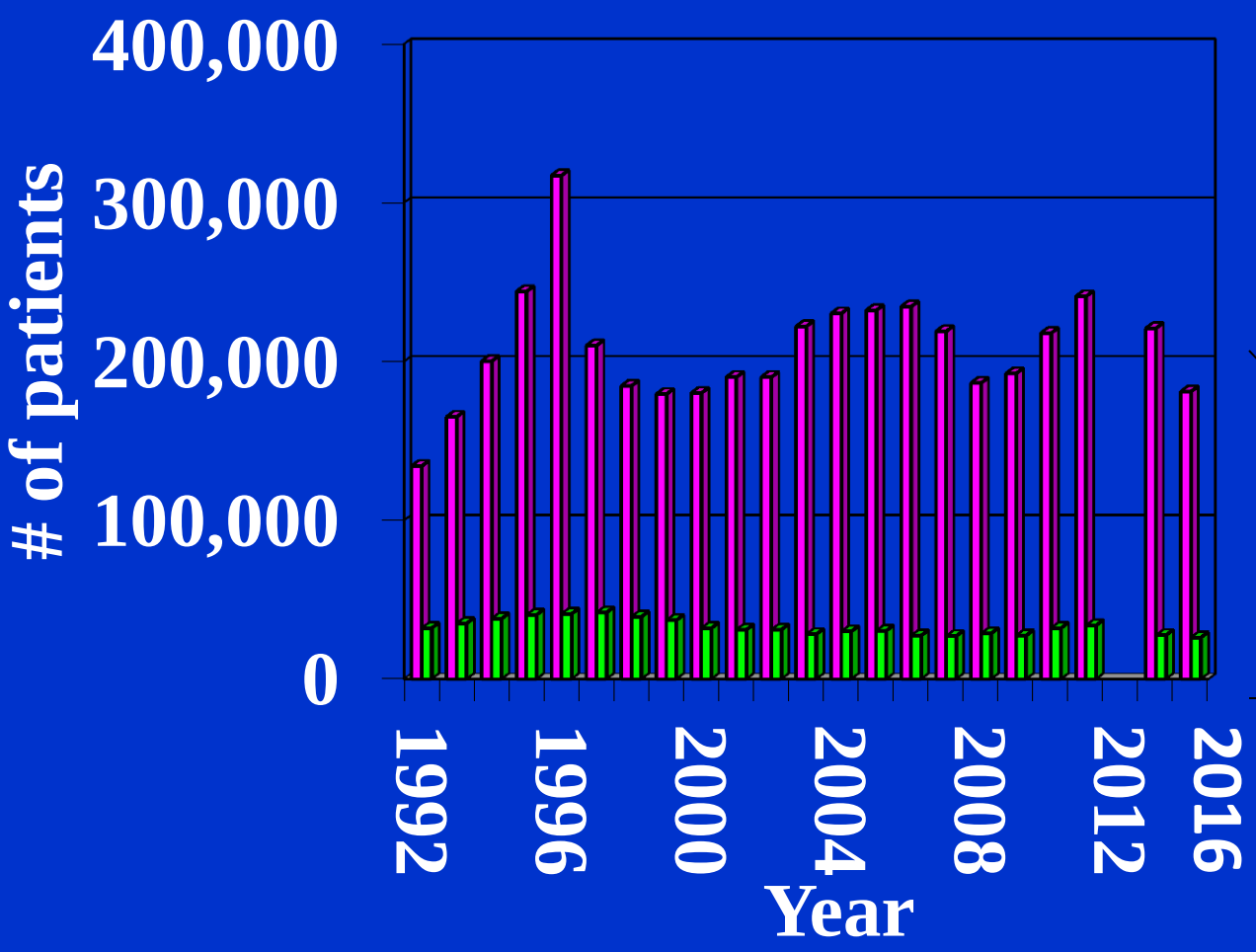
BUFFALO, NY

GOALS

- Epidemiology, Screening and Prevention
- Risk Stratification
- Treatment of Early and High Risk Disease
- Hormonal Therapy
- Treatment of Advanced Disease

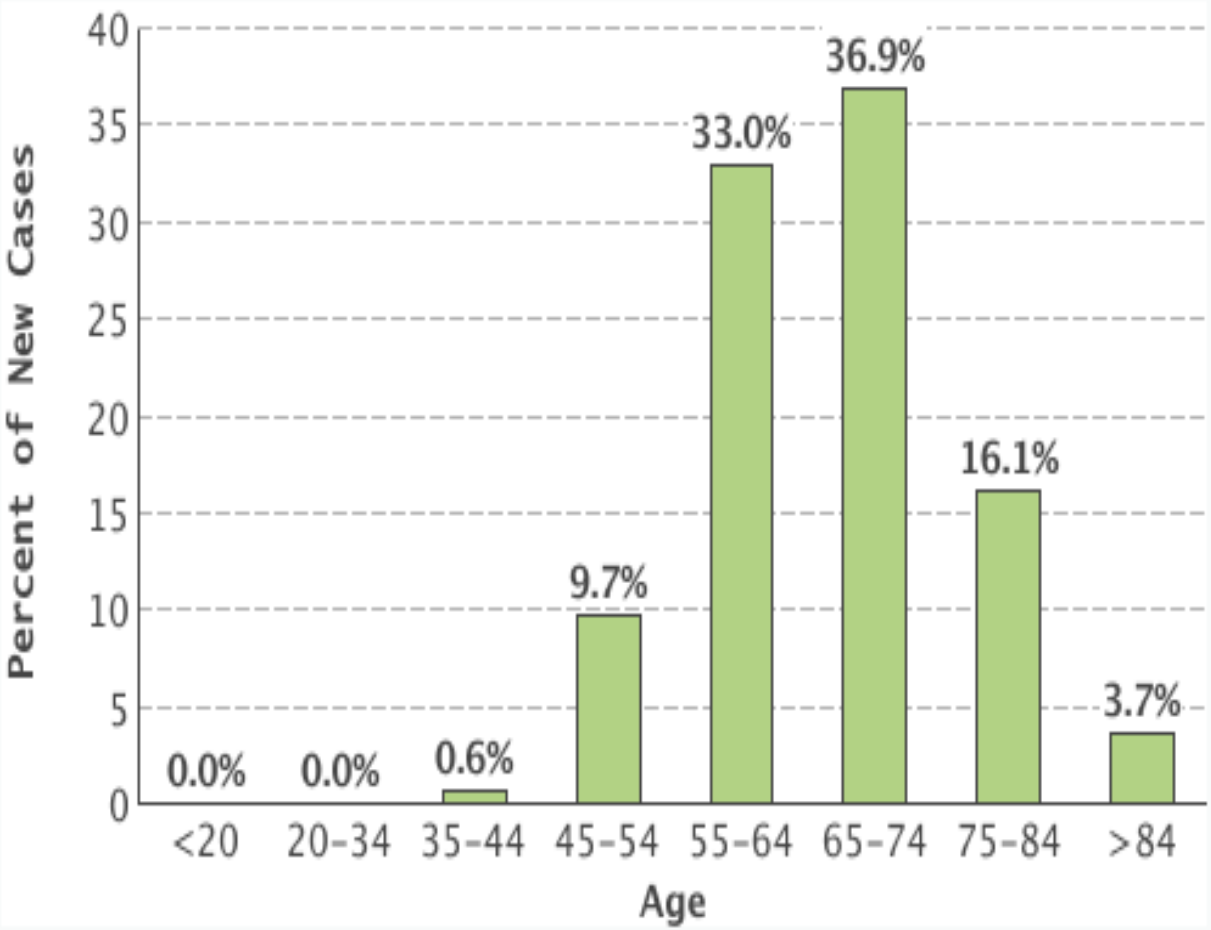
Prostate Cancer Incidence



180,890 cases

26,120 deaths

Percent of New Cases by Age Group: Prostate Cancer



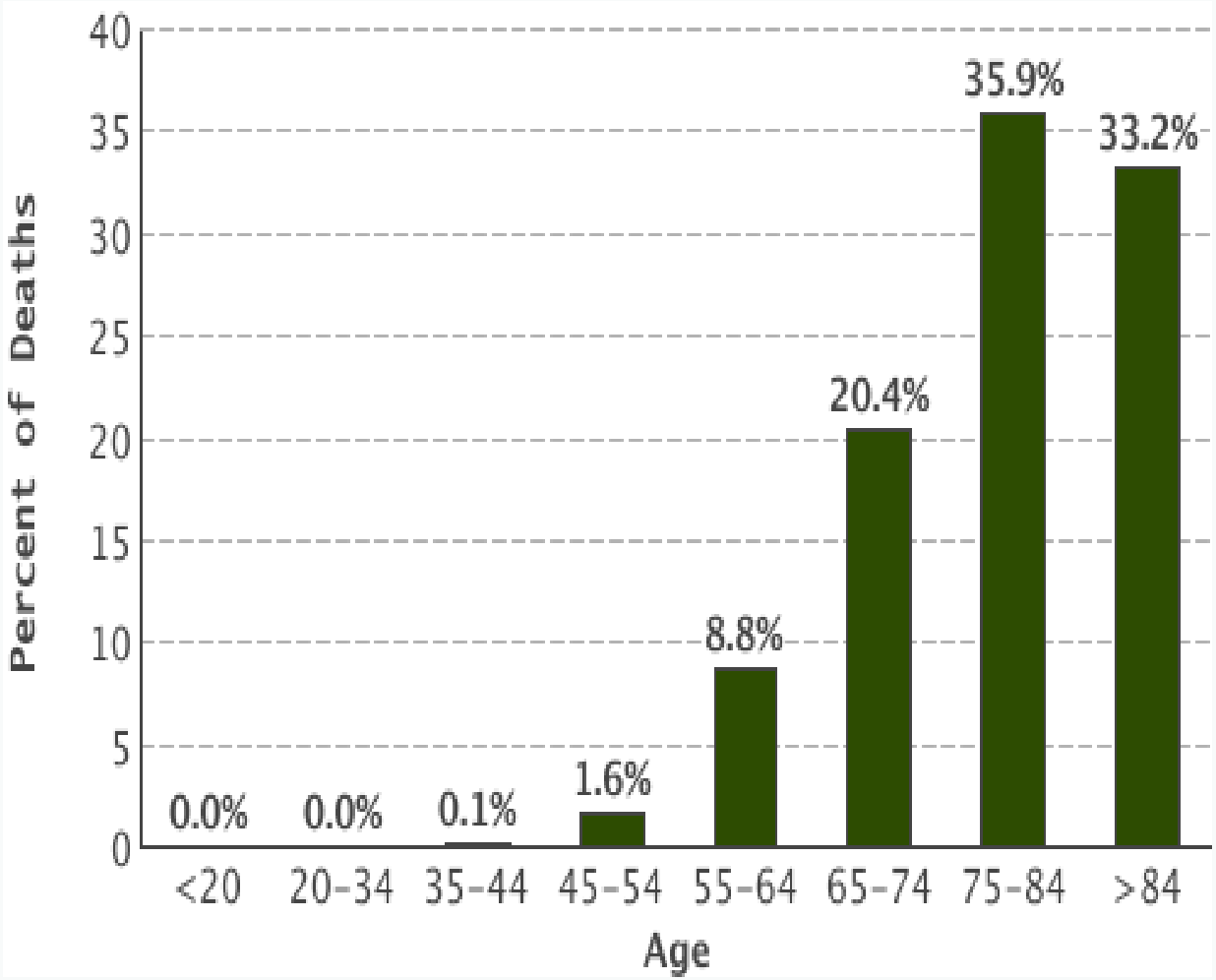
Prostate cancer is most frequently diagnosed among men aged 65-74.

Median Age At Diagnosis

66

SEER 18 2008-2012, All Races, Males

Percent of Deaths by Age Group: Prostate Cancer



The percent of prostate cancer deaths is highest among men aged 75–84.

Median Age At Death
80

U.S. 2008–2012, All Races, Males

Chemoprevention

~~5 ARIs reduce risk of prostate cancer but long term effects are not yet known~~

- FDA has chosen not to approve
- Long term effect on survival and toxicity?

Does PSA based Screening Reduce Mortality?

- PLCO
- ERSPC study
- Göteborg study

Randomized Screening Studies for Prostate Cancer

- PLCO (NEJM 2009)
  - 150,000 men
  - 52% contamination
  - Median follow-up of 7 years
  - **No difference in prostate cancer mortality**
- European Screening Study (NEJM 2009)
  - 162,243 men
  - Median follow up of 9 years
  - **20% reduction in prostate cancer mortality p=0.04**
  - **NNT- 48 needed to be treated to prevent 1 death**
- Göteborg screening trial (Lancet Oncology 2010)
  - 20,000 men
  - Median follow-up of 14 years
  - **44% reduction in prostate cancer mortality (p=0.0002).**
  - **NNT-12 needed to be treated to prevent 1 death**

Conclusions

- Low mortality of prostate cancer in first 10 years (few events)
- PSA screening probably reduces mortality but longer follow-up needed
- Apparent large amount of over-diagnosis and overtreatment (at least as seen in first 10 years)

Impact of USPTF on Screening

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

National Prostate Cancer Screening Rates After the 2012 US Preventive Services Task Force Recommendation Discouraging Prostate-Specific Antigen–Based Screening

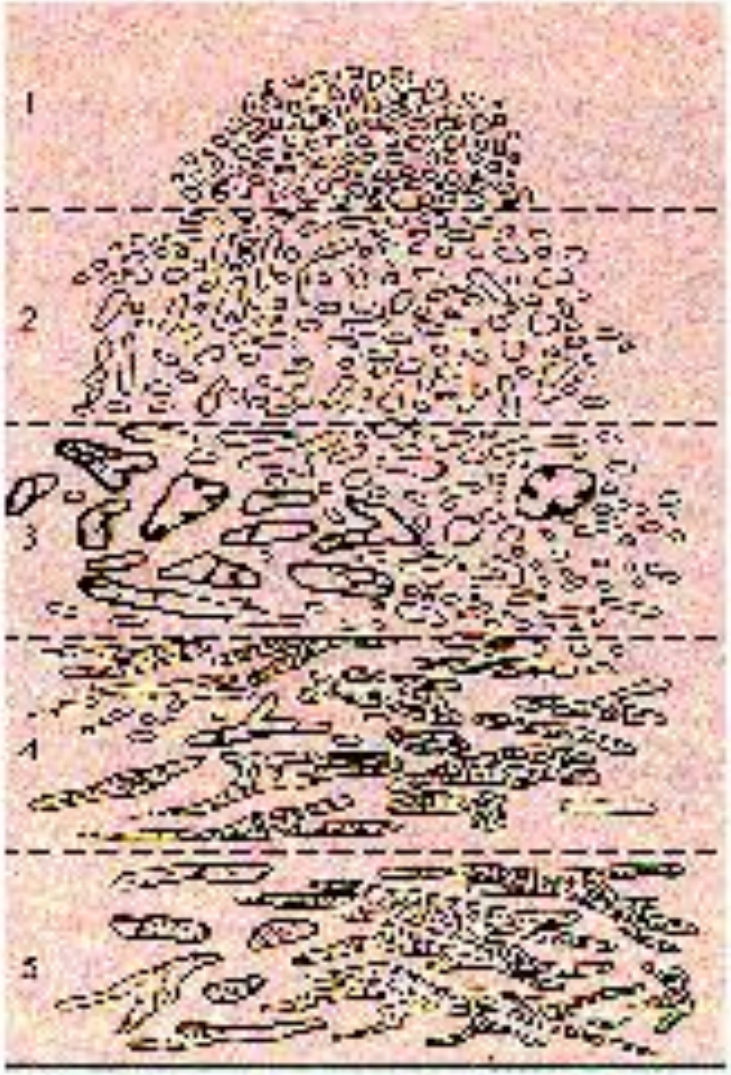
Michael W. Drazer, Dezheng Huo, and Scott E. Eggener

Presented by: Fred Saad MD FRCS

Diagnosis Suspected

- Abnormal PSA
- Abnormal DRE
- CaP detected on TURP

Gleason's Pattern

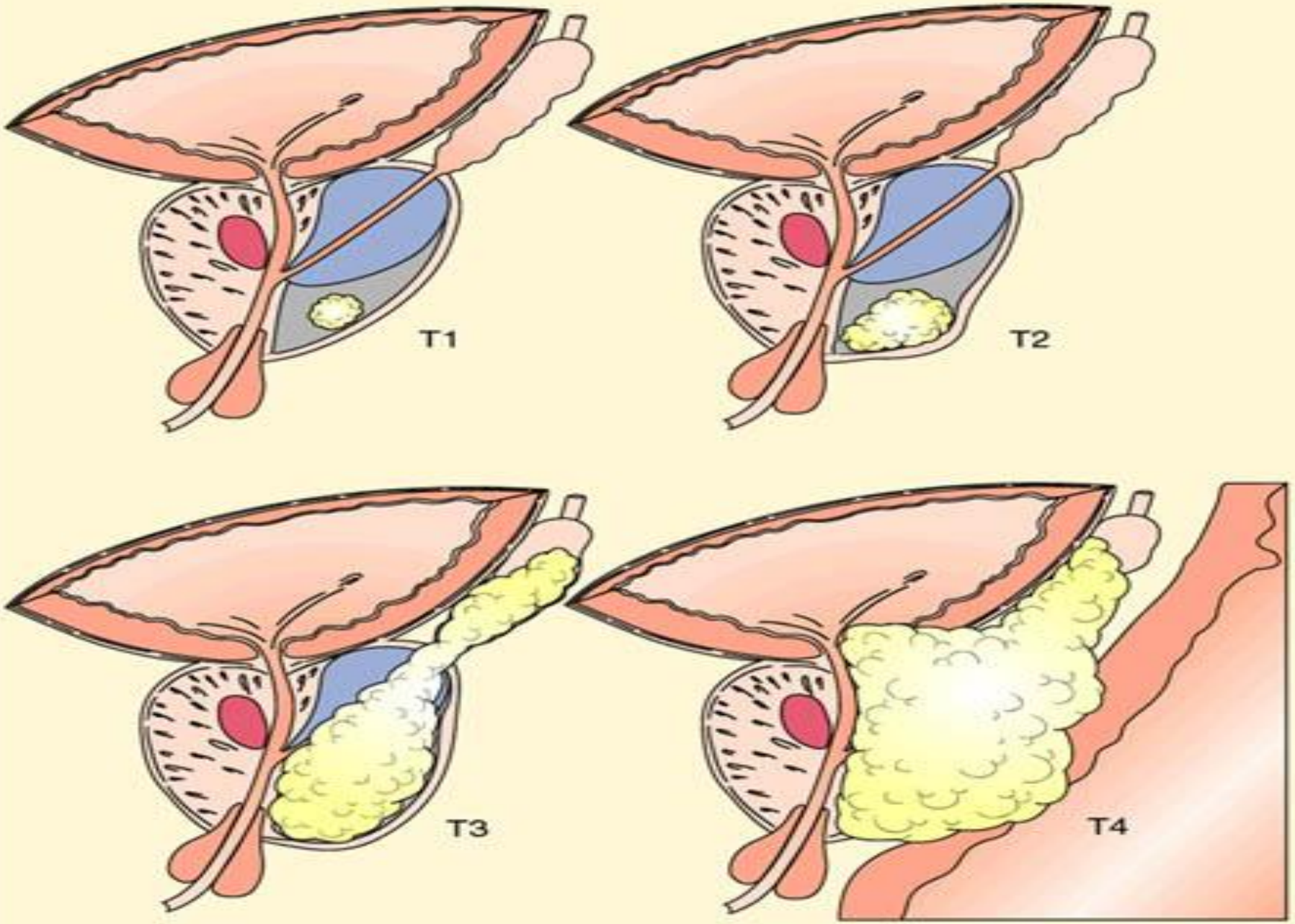


1. Small, uniform glands
2. More stroma between glands
3. Distinctly infiltrative margins
4. Irregular masses of neoplastic glands
5. Only occasional gland formation

Well differentiated

Moderately differentiated

Poorly diff./ Anaplastic


T1
T2
T3
T4

Risk Groups

Low Risk	PSA<10 Gleason<7 Stage T1c or T2a	and and
Intermediate Risk	PSA 10-20 Gleason 7 Stage T2b	or or
Poor Risk	PSA >20 Gleason >7 Stage T2c	or or

Staging-Metastatic vs Non-Metastatic

- Bone scan and CT scan
  - Only required in intermediate and poor risk patients

ONCOTYPE DX

- Genomic Health
- 17 gene signature
- Stratifying Low risk and Intermediate risk disease

Treatment Choices

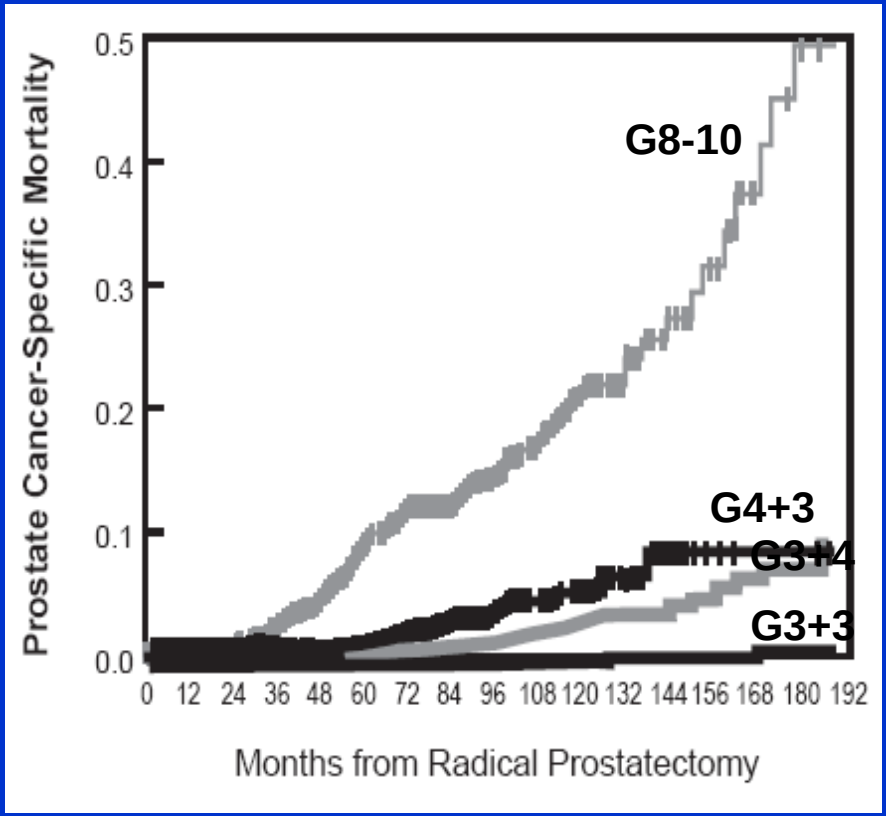
- No treatment-Active surveillance
- Radical prostatectomy
- Radiation
  - External beam-conformal
  - Brachytherapy-seeds
  - Neutrons
  - Protons
- Hormonal therapy
- Combination therapies

Outcome of Surgically Treated Patients

- The cohort: 24,441 patients who underwent RP between 1987-2005 at:
  - Cleveland Clinic
  - MSKCC
  - Baylor College of Medicine
  - University of Michigan
  - JHH
- All pathological specimens reviewed by genitourinary pathologists at each institution
- Endpoint: Prostate cancer mortality

Stephenson et al
J. Clin Onc 2009

Outcome of Treated Patients



- **Gleason 8-10**: 10% of all cases
  - 49% 15-year PCSM
  - 45% of all cancer deaths
- **Gleason 7**: 40% of all cases
  - 8% 15-year PCSM
  - 50% of all cancer deaths
- **Gleason 6** 50% of all cases
  - <1% 15-year PCSM
  - 1 of 3756 patients with organ-confined, Gleason 6 cancer has died of prostate cancer

Long term outcome of AS

VOLUME 33 · NUMBER 3 · JANUARY 20 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

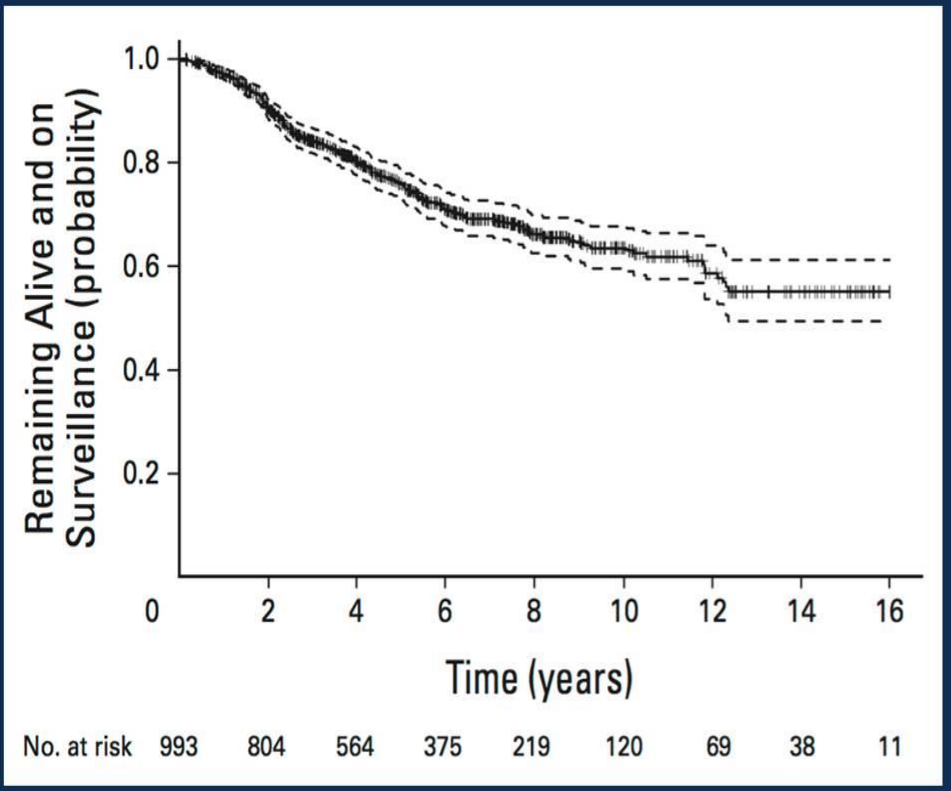
Long-Term Follow-Up of a Large Active Surveillance Cohort of Patients With Prostate Cancer

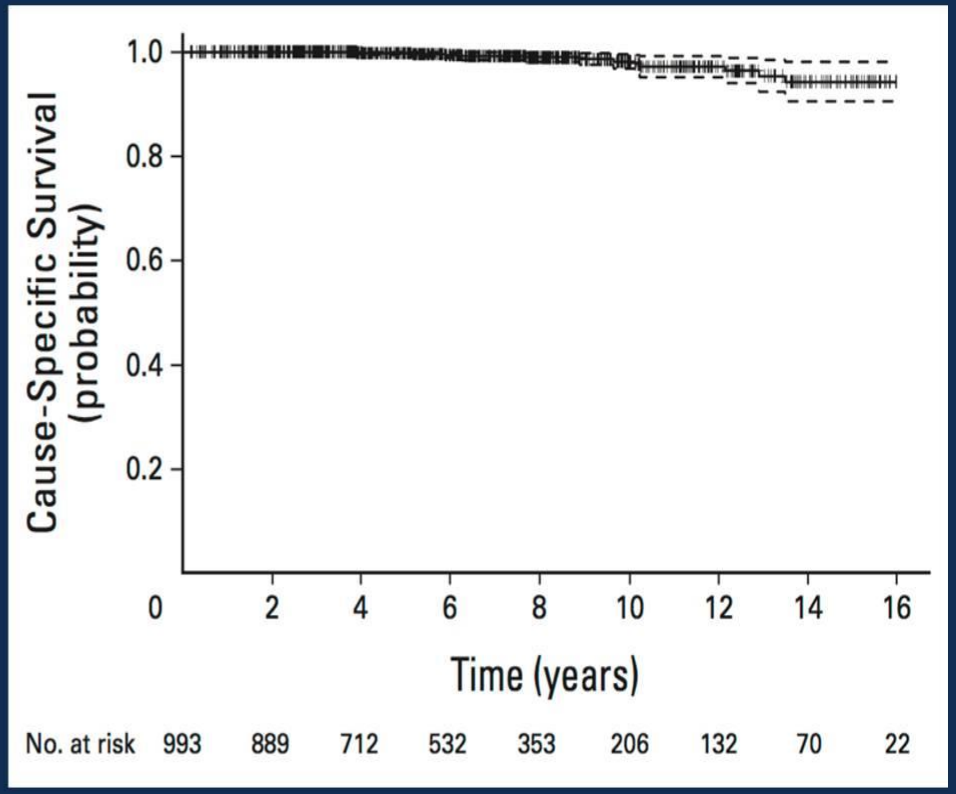
Laurence Klotz, Danny Vesprini, Perakaa Sethukavalan, Vibhuti Jethava, Liying Zhang, Suneil Jain, Toshihiro Yamamoto, Alexandre Mamedov, and Andrew Loblaw

PRESENTED AT: 2016 Genitourinary Cancers Symposium

Presented by:

Remaining on AS CS survival



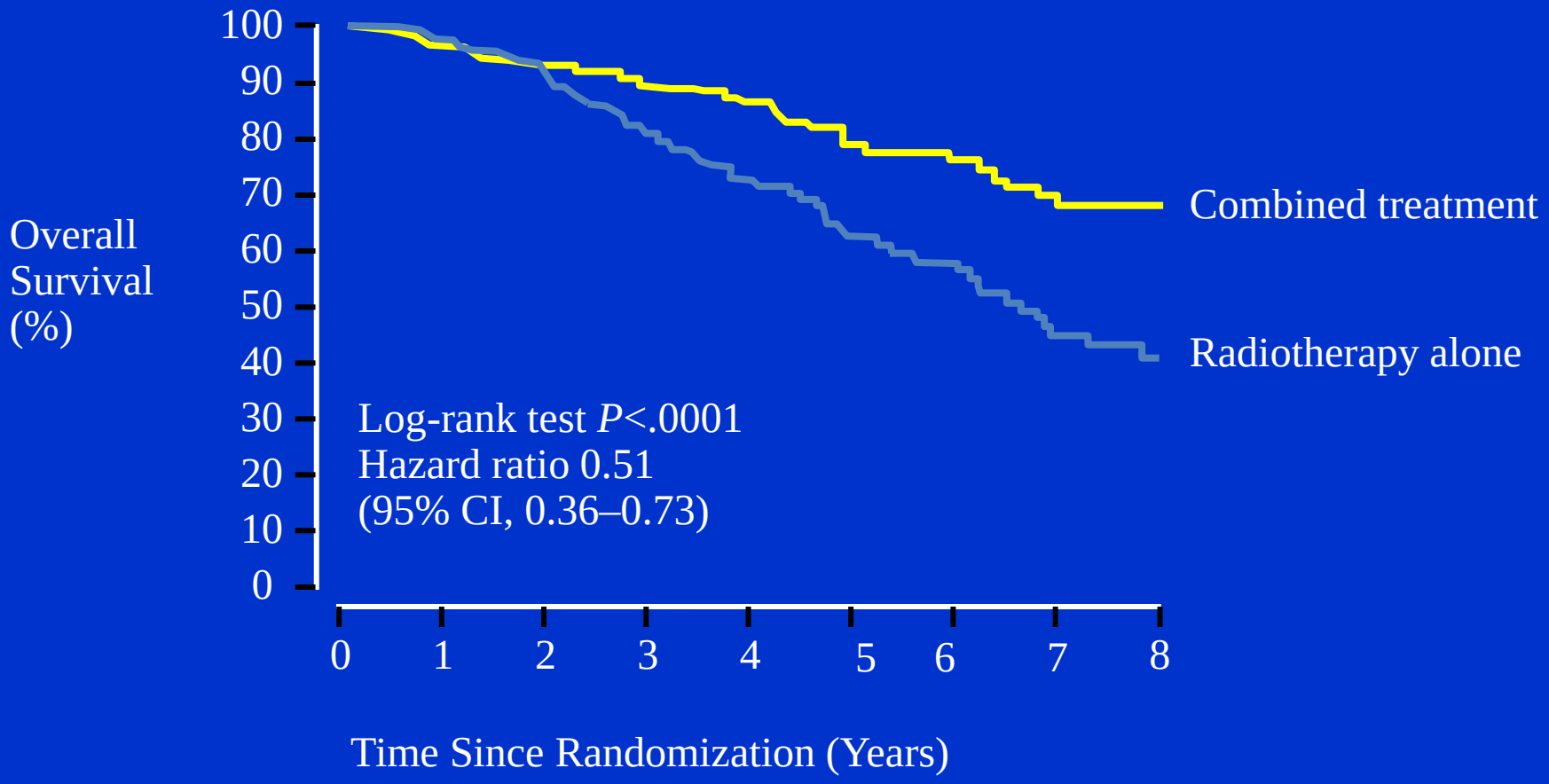


Conclusions

- Active surveillance for favorable-risk prostate cancer is feasible and seems safe in the 15-year time frame.
- 2.8% developped metastatic disease, 1.5% died of PCa
- Mortality rate is consistent with expected mortality in favorable-risk patients managed with initial definitive intervention.

Multimodality Treatment: High Risk Disease

EBRT vs EBRT + 3 Years HT: EORTC Trial 2002



Bolla M, et al. *Lancet*. 2002;360:103-106.

Summary-Locally Advanced Tumors: XRT +ADT

- Overall survival

  3 years or longer provides benefit

- Prolonged duration needs to be balanced with side effects

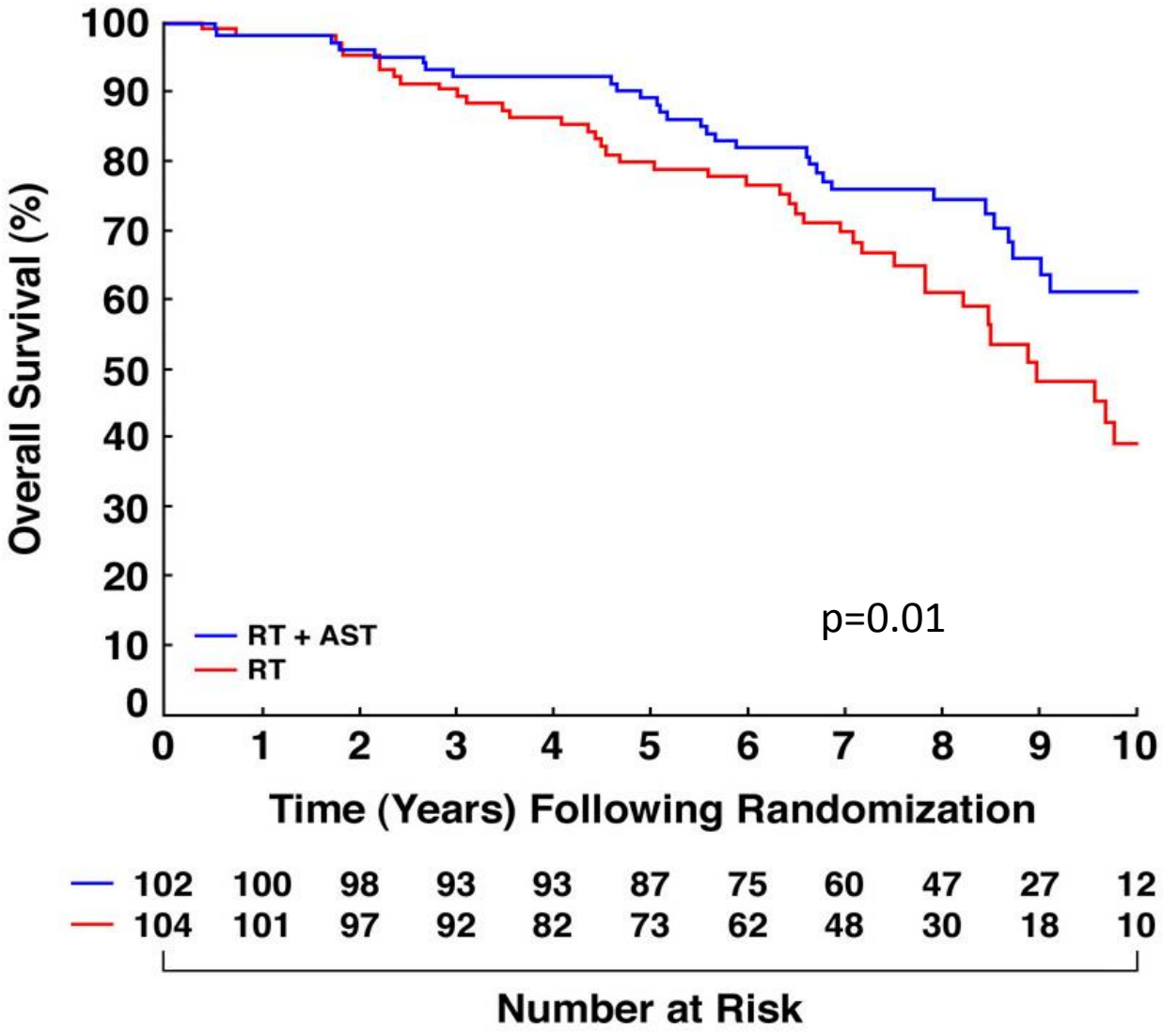
Multimodality Therapy: What about Patients with Intermediate and High Risk but Localized Disease (T1-2)

XRT vs. XRT + ADT for Intermediate and High Risk Patients

- 205 patients with PSA> 10 or Gleason >6
- Randomized to XRT or XRT + 6 months of ADT
- Median follow-up 7.6 years
- Overall survival HR=1.8 (p=0.01)
- PCSM HR=4.1 (p=0.01)

D'Amico et al JAMA 2008

Overall Survival

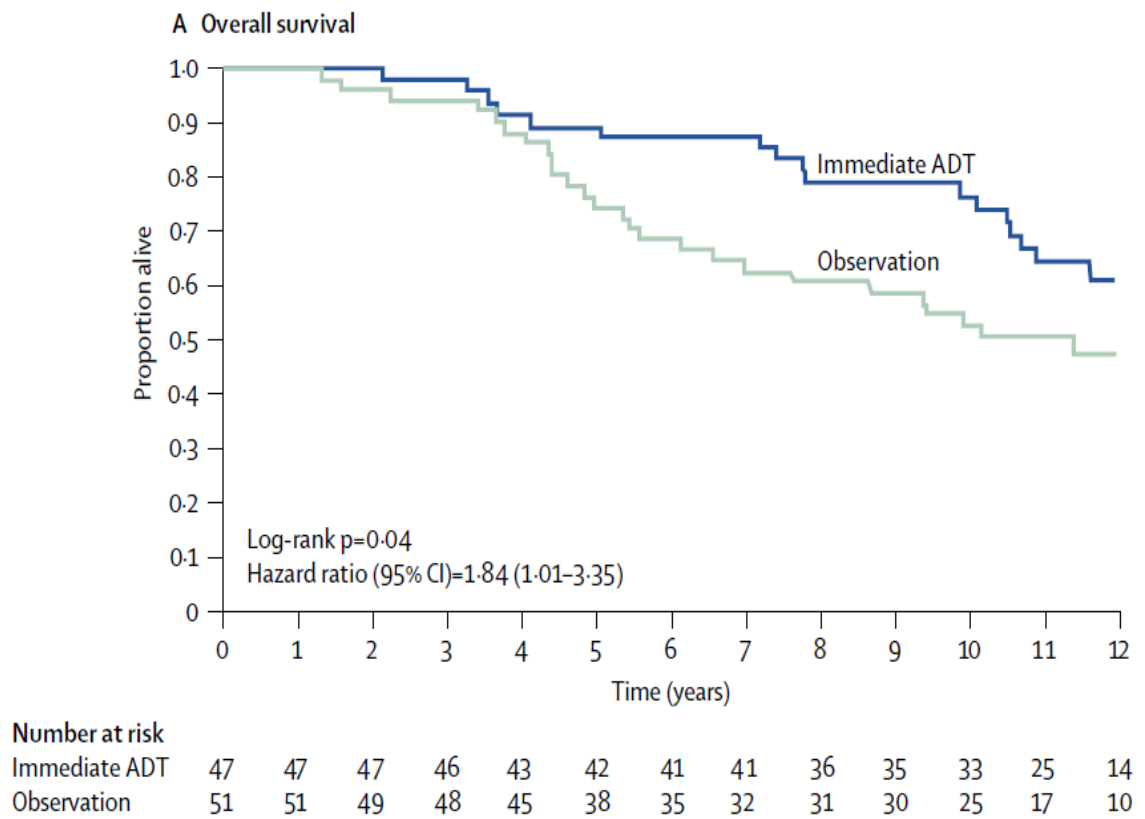


D'Amico et al JAMA 2008

Adjuvant Therapy

- Adjuvant radiation i.e. radiation post radical prostatectomy in high risk patients
  - Two studies demonstrating OS benefit
  - ? Should be considered standard of care
- Adjuvant chemotherapy
  - No proven benefit
  - Several randomized trials underway (docetaxel)
- Adjuvant ADT
  - No proven benefit

Adjuvant Hormone Ablation
ECOG 3886: Results at 12 Years



Randomized trial

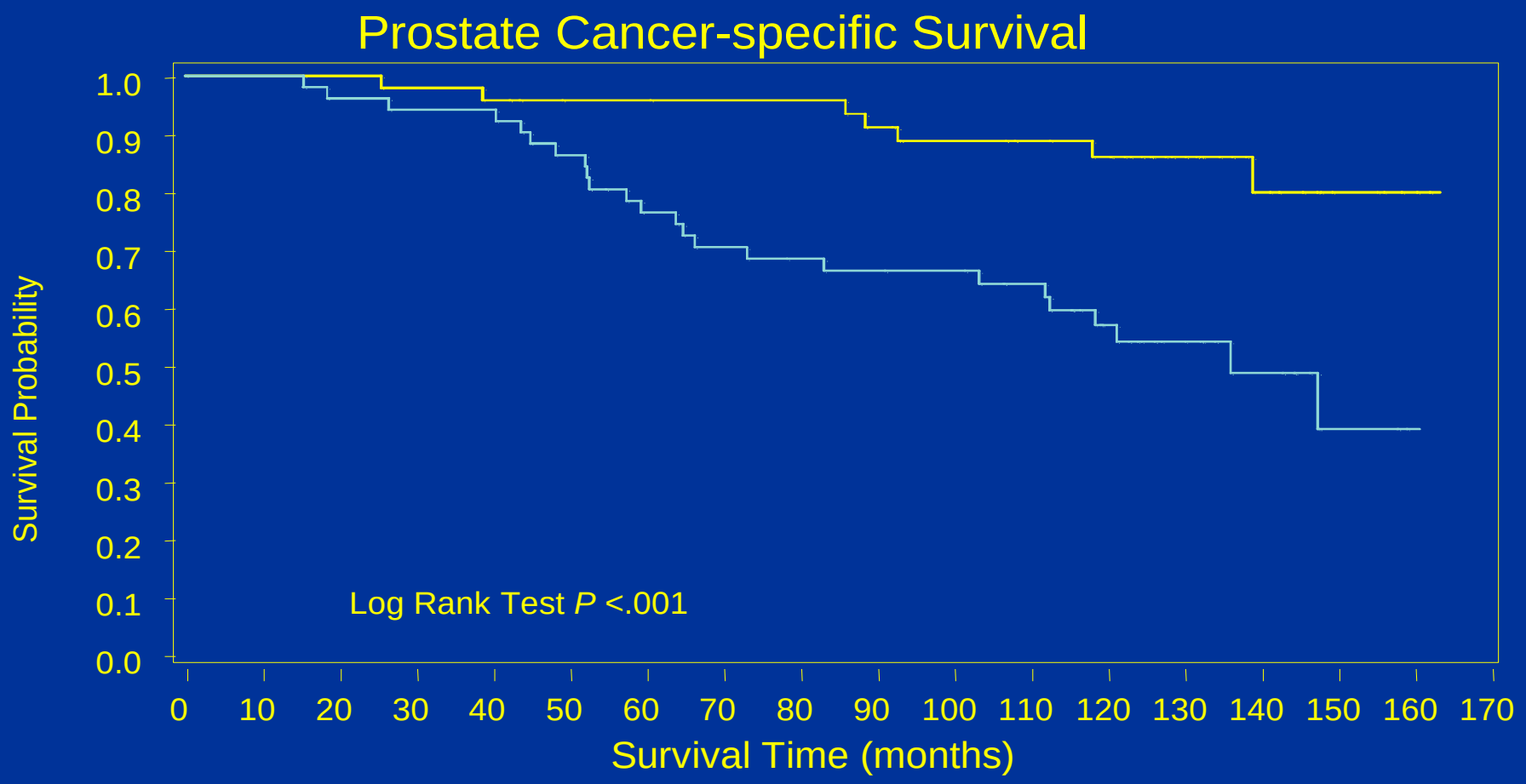
98 patients

Nodal metastases

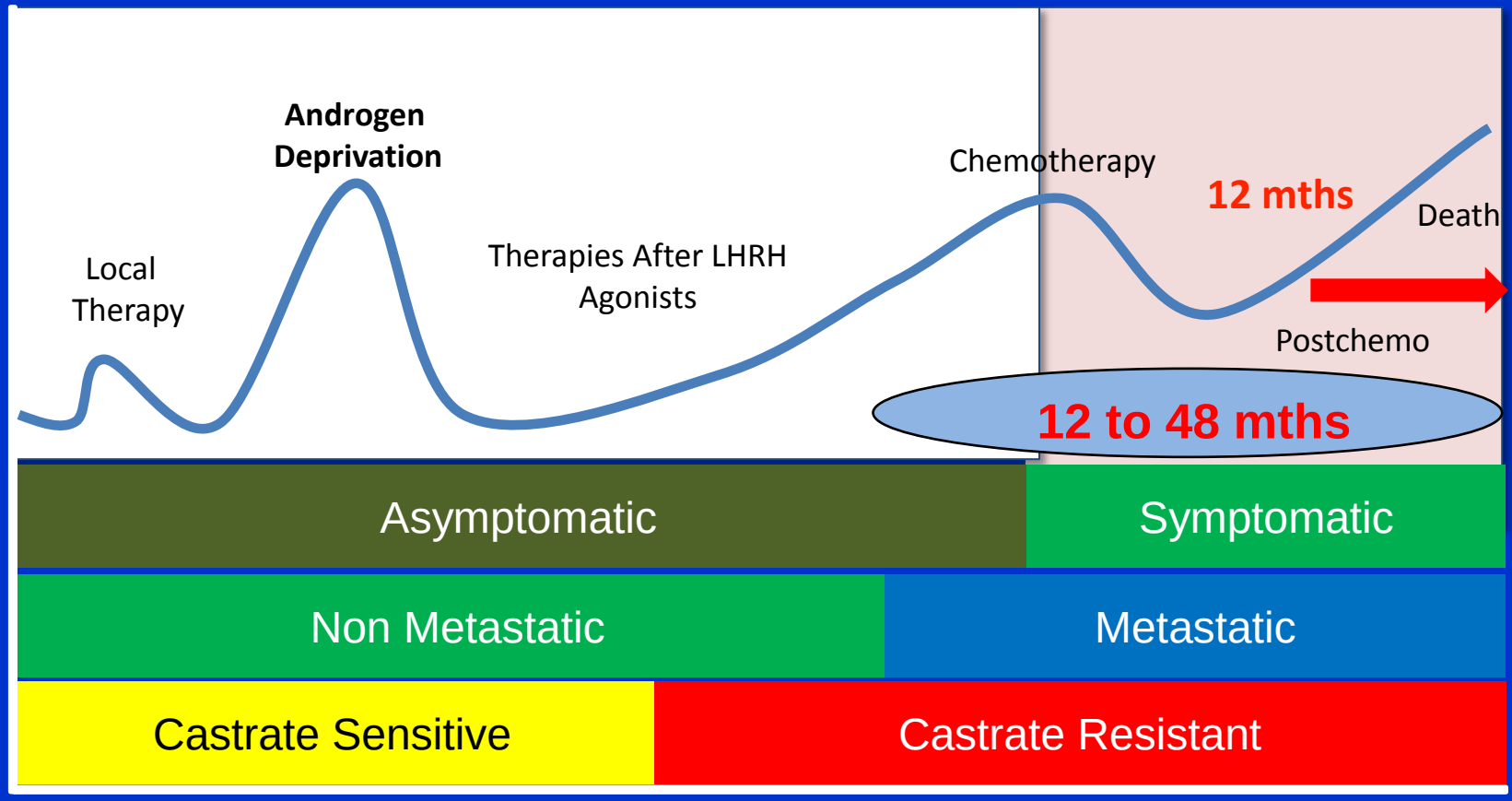
Immediate hormonal therapy improves survival in node positive patients

Messing EM, et al. Lancet Oncol. 2006

Adjuvant Hormone Ablation
ECOG 3886: Results at 10 Years



Natural History of Prostate Cancer

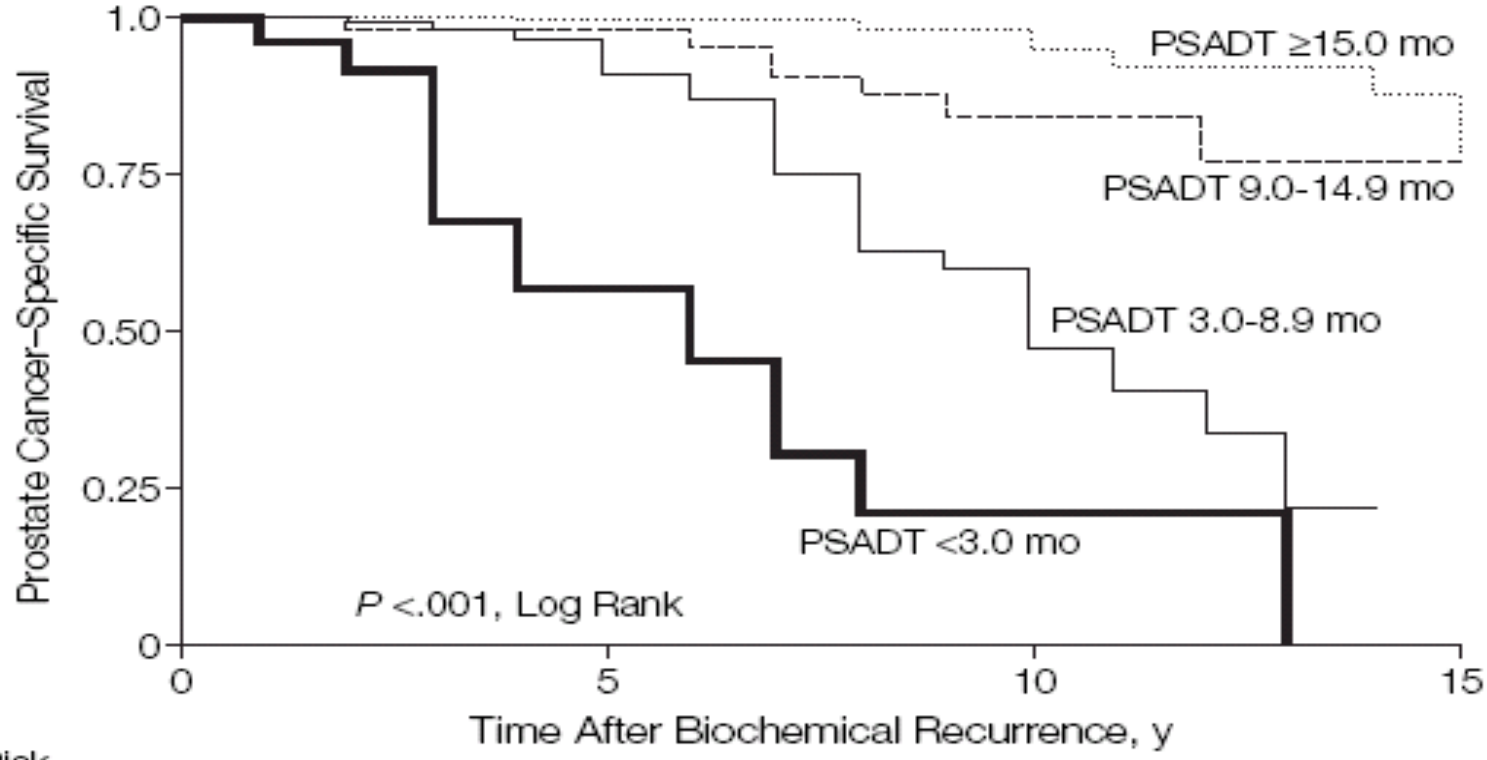


Natural History Of Rising PSA

- 304 men relapsed after surgery
- No hormones until (+) bone scan
- Time to PSA rise, Gleason, PSADT were predictors of survival

Pound JAMA 1999

Patients with a Rising PSA-Importance of PSADT



No. at Risk PSADT, mo				
<3.0	23	10	2	0
3.0-8.9	119	85	19	0
9.0-14.9	79	51	19	3
≤15	158	113	52	9

Freedland SJ, et al. *JAMA*. 2005

Does local control matter in locally advanced prostate cancer?

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

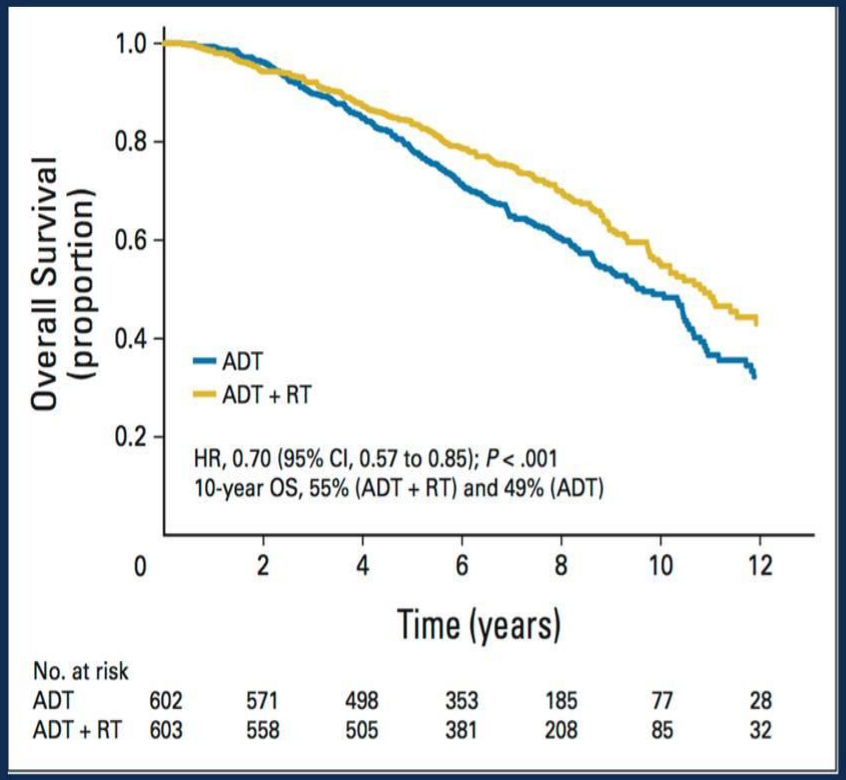
Final Report of the Intergroup Randomized Study of Combined Androgen-Deprivation Therapy Plus Radiotherapy Versus Androgen-Deprivation Therapy Alone in Locally Advanced Prostate Cancer

Malcolm D. Mason, Wendy R. Parulekar, Matthew R. Sydes, Michael Brundage, Peter Kirkbride, Mary Gospodarowicz, Richard Cowan, Edmund C. Kostashuk, John Anderson, Gregory Swanson, Mahesh K.B. Parmar, Charles Hayter, Gordana Jovic, Andrea Hiltz, John Hetherington, Jinka Sathya, James B.P. Barber, Michael McKenzie, Salah El-Sharkawi, Luis Souhami, P.D. John Hardman, Bingshu E. Chen, and Padraig Warde

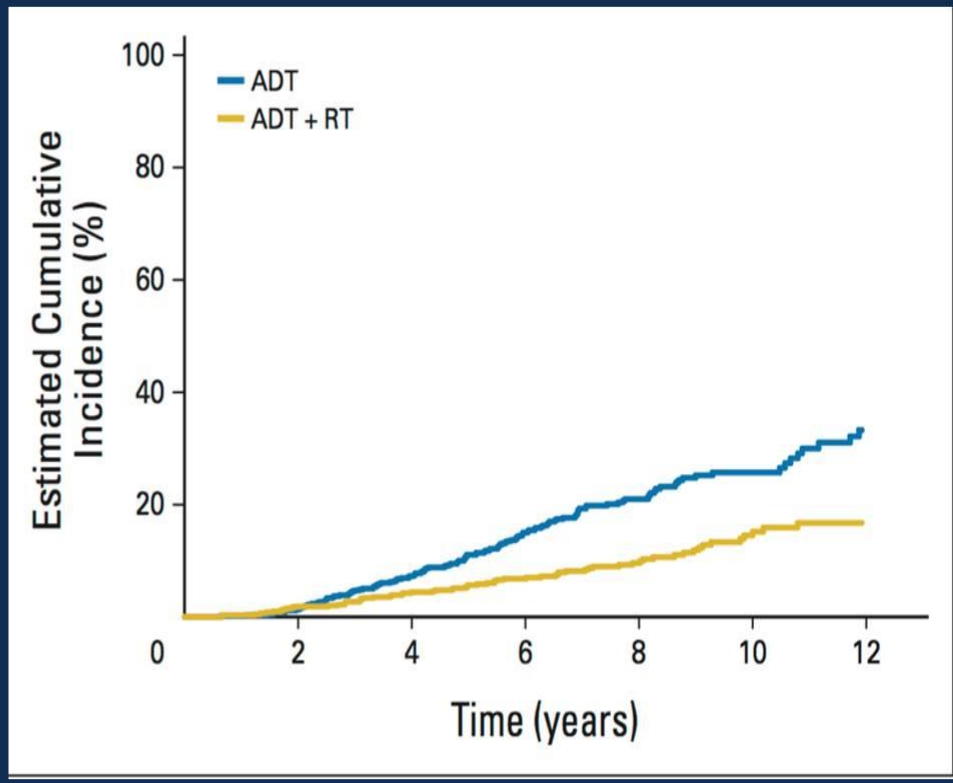
PRESENTED AT: 2016 Genitourinary Cancers Symposium

Presented by:

Overall survival



CS survival



Conclusion

- Role of radiation therapy clearly established for high risk and locally advanced prostate cancer
- Evidence mounting for metastatic patients
- Mounting evidence for surgery but RCT's not available

Androgen-Deprivation Therapy: Definition

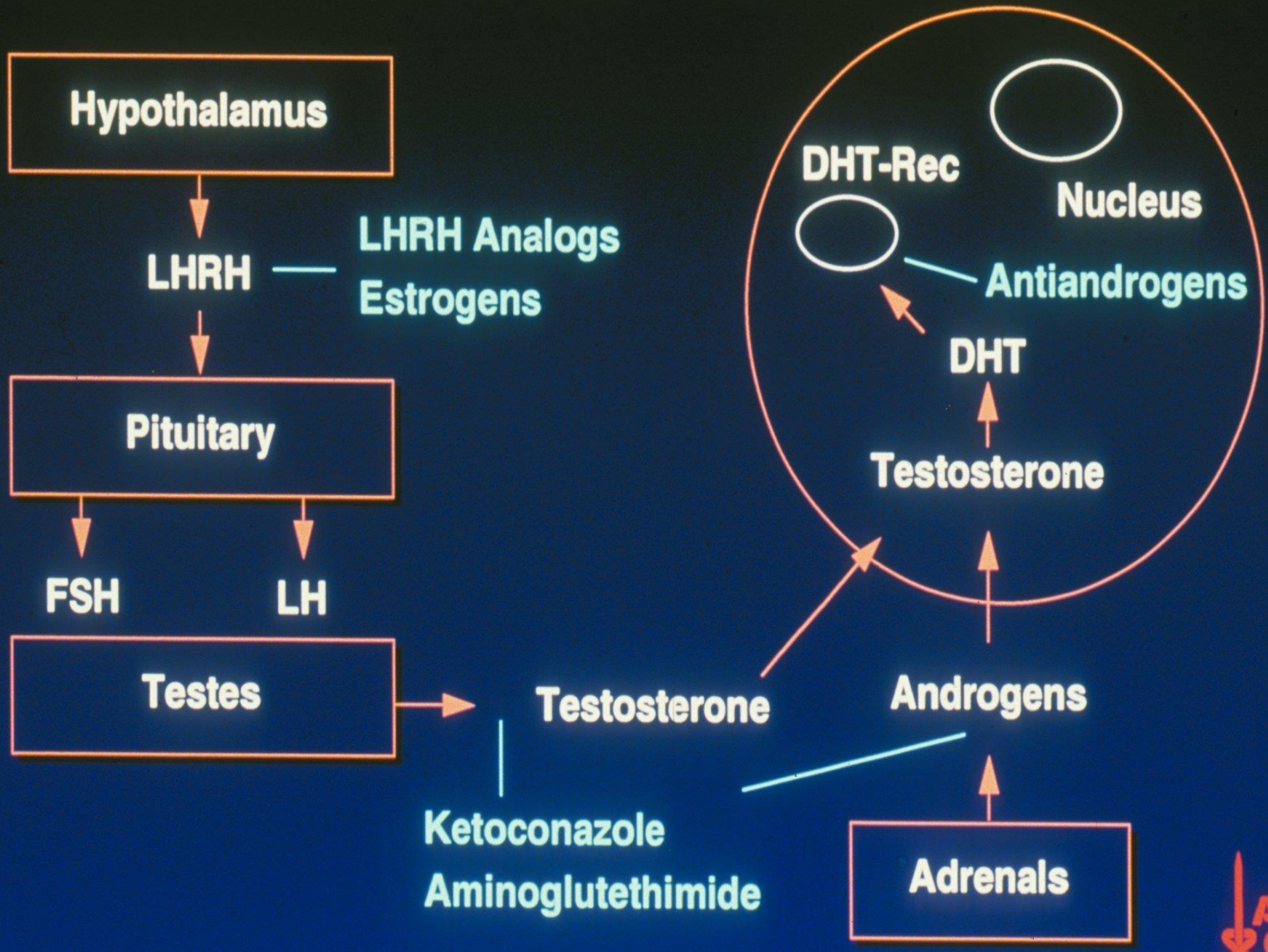
Androgen-deprivation therapy (ADT) is any treatment that blocks interaction of androgen with the androgen receptor

- Orchiectomy
- LHRH agonists
- LHRH antagonists
- Estrogens
- Combined androgen blockade
- Antiandrogen monotherapy

Existing therapies do not adequately suppress adrenal or intratumoral production of androgen

LHRH = luteinizing hormone-releasing hormone.

Endocrine Therapy of Prostate Cancer

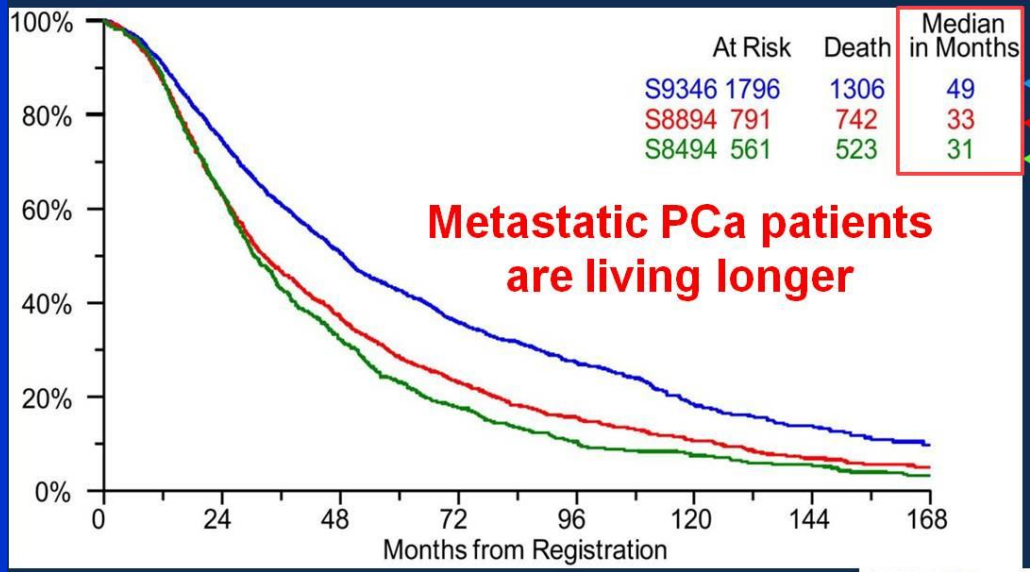


ADT: Indications

- Indications
  - Newly diagnosed metastatic disease
  - Adjuvant therapy of node positive disease discovered at prostatectomy
  - Combined with radiotherapy in patients with intermediate/high-risk disease
- Use of ADT in patients with biochemical progression is controversial

Metastatic Prostate Cancer

M1 Prostate Cancer *Then & NOW*

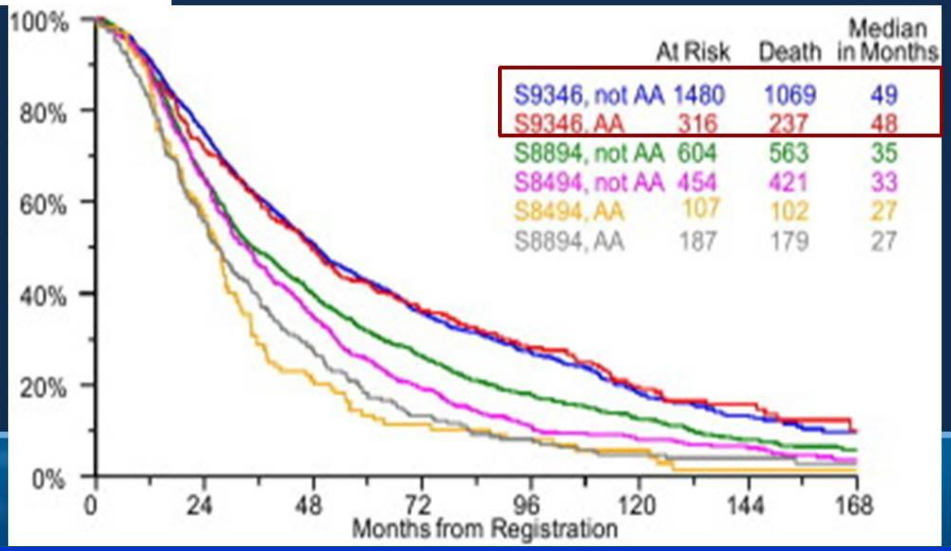


1990s-2000 + (PSA era)

Late 80s-early 1990s

1980

Racial Gap has decreased



Tangen M, Hussain MH, Higano CS, et al: J Urol 2012

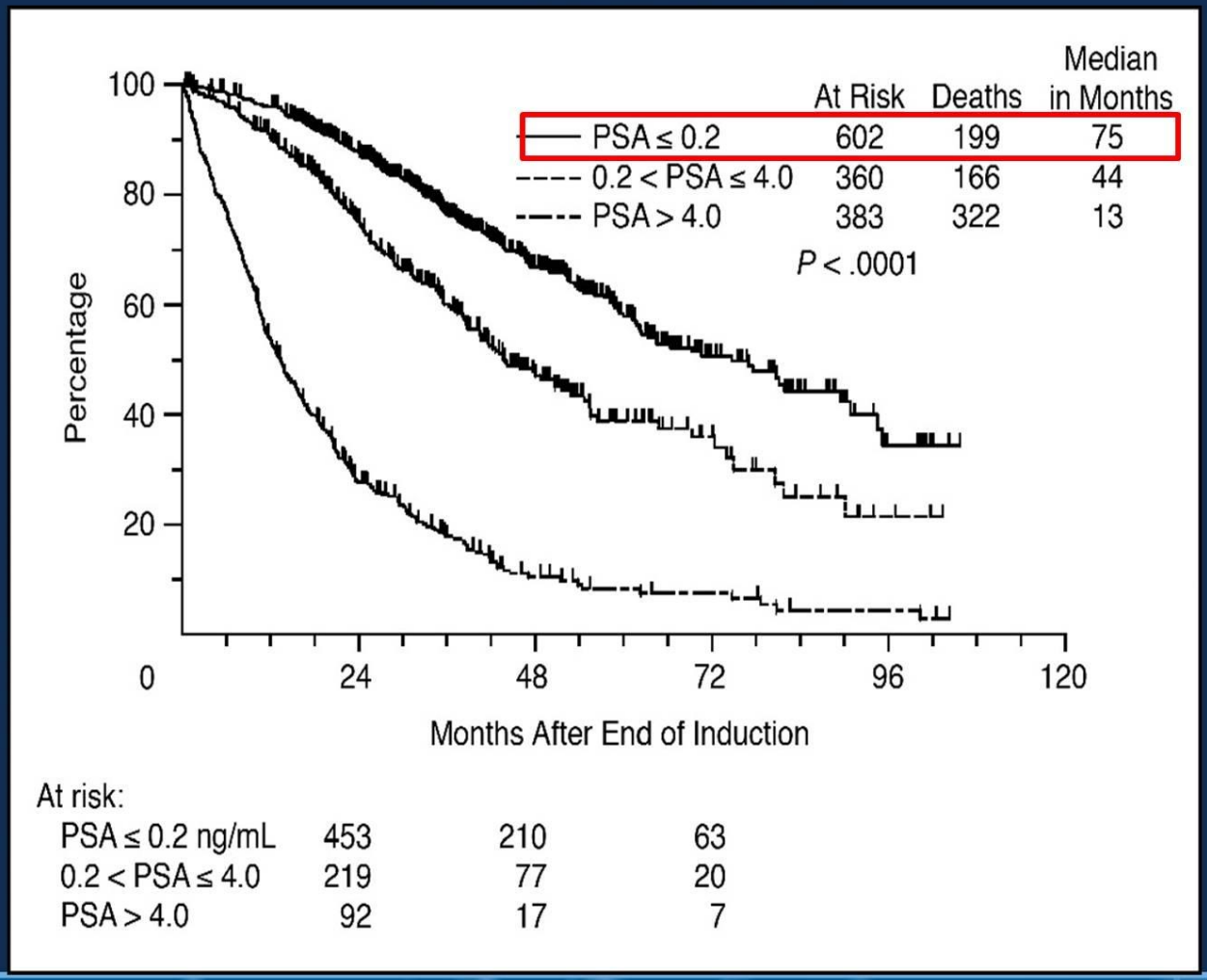
PRESENTED AT: 2016 Genitourinary Cancers Symposium

What is a good response to ADT?

- SWOG 9346 Intermittent ADT Trial
- 1345 eligible patients
- Level of PSA after 8 months of ADT

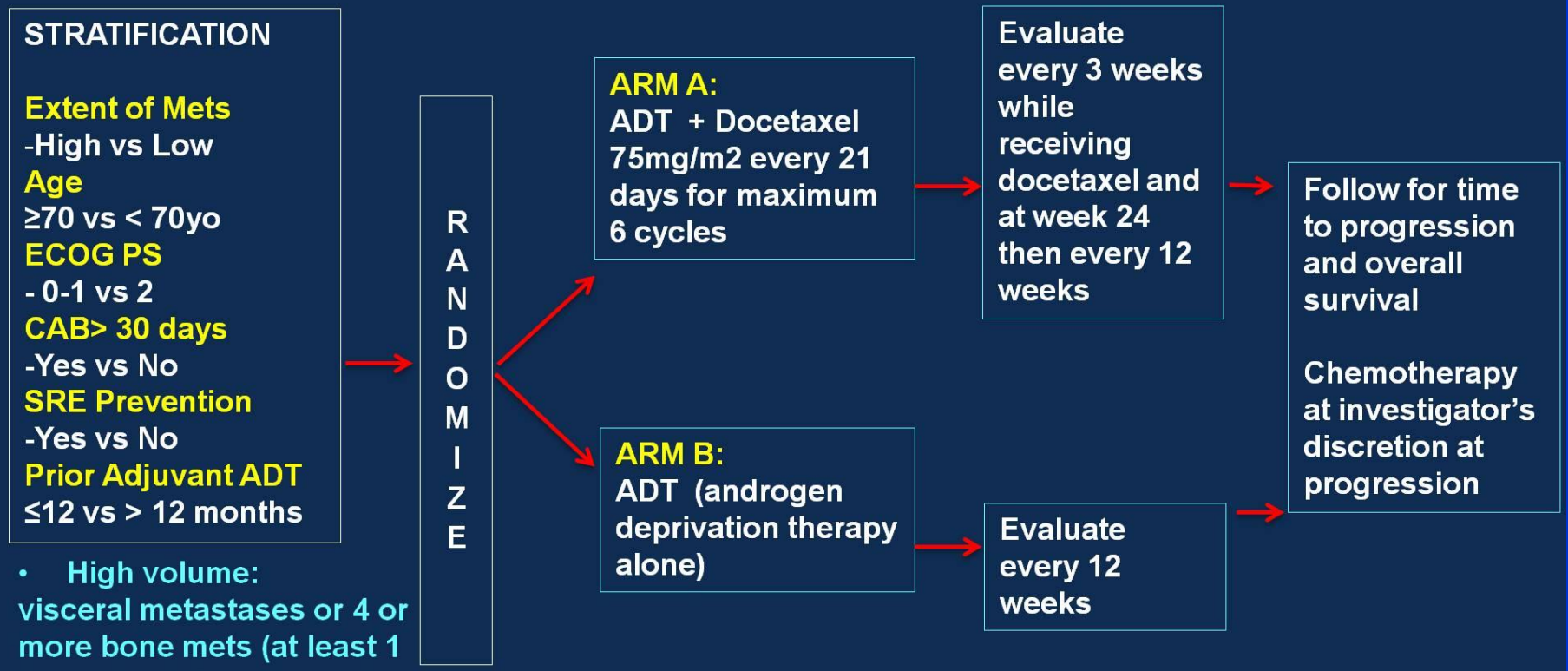
Hussain et al J.Clin Onc 2007

S9346: "A PSA of ≤ 4 and < 0.2 ng/mL after 7 Months of ADT is A Strong Predictor of Overall Survival"



Hussain et al. J Clin Oncol; 2006

E3805:CHAARTED: ChemoHormonal Therapy vs Androgen Ablation Randomized Trial

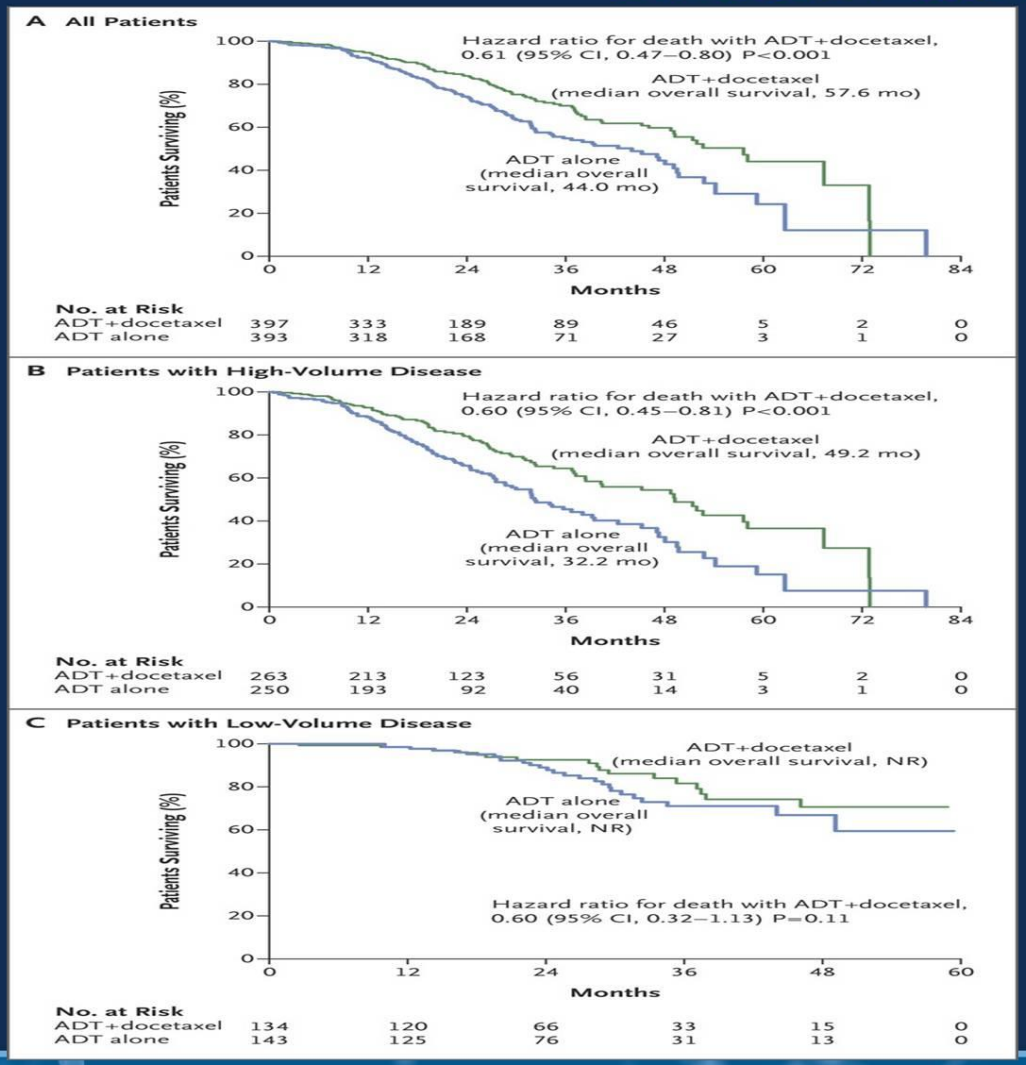


- High volume: visceral metastases or 4 or more bone mets (at least 1 beyond pelvis and vertebral column)
- At inception, only pts with high volume disease were to be accrued

- ADT allowed up to 120 days prior to randomization.
- Intermittent ADT dosing was not allowed
- Standard dexamethasone premedication but no daily prednisone

Sweeney C, et al ASCO 2014 – NEJM 2015

Overall Survival: All Patients & by Metastatic Disease Extent



N=790
Median OS:
ADT + D: 57.6 months
ADT alone: 44.0 months
HR=0.61 (0.47-0.80)
p=0.0003

N=514
Median OS:
ADT + D: 49.2 months
ADT alone: 32.2 months

HR=0.60 (0.45-0.81)
p=0.0006

N=276
Median OS:
ADT + D: Not reached
ADT alone: Not reached
HR=0.63 (0.34-1.17)
p=0.1398

Sweeney CJ et al. N Engl J Med 2015

E3805:CHAARTED
Secondary End Points

Table 2. Secondary End Points.

End Point	ADT plus Docetaxel (N=397)	ADT Alone (N=393)	P Value	Hazard Ratio (95% CI)
PSA level <0.2 ng/ml at 6 mo — no. (%)	127 (32.0)	77 (19.6)	<0.001	
PSA level <0.2 ng/ml at 12 mo — no. (%)	110 (27.7)	66 (16.8)	<0.001	
Time to castration-resistant prostate cancer — mo*				
Median	20.2	11.7	<0.001	0.61 (0.51–0.72)
95% CI	17.2–23.6	10.8–14.7		
Time to clinical progression — mo†				
Median	33.0	19.8	<0.001	0.61 (0.50–0.75)
95% CI	27.3–41.2	17.9–22.8		

* The time to castration-resistant prostate cancer was the time until documented clinical or serologic progression with a testosterone level of less than 50 ng per deciliter (or source documentation of medical castration or surgical castration).

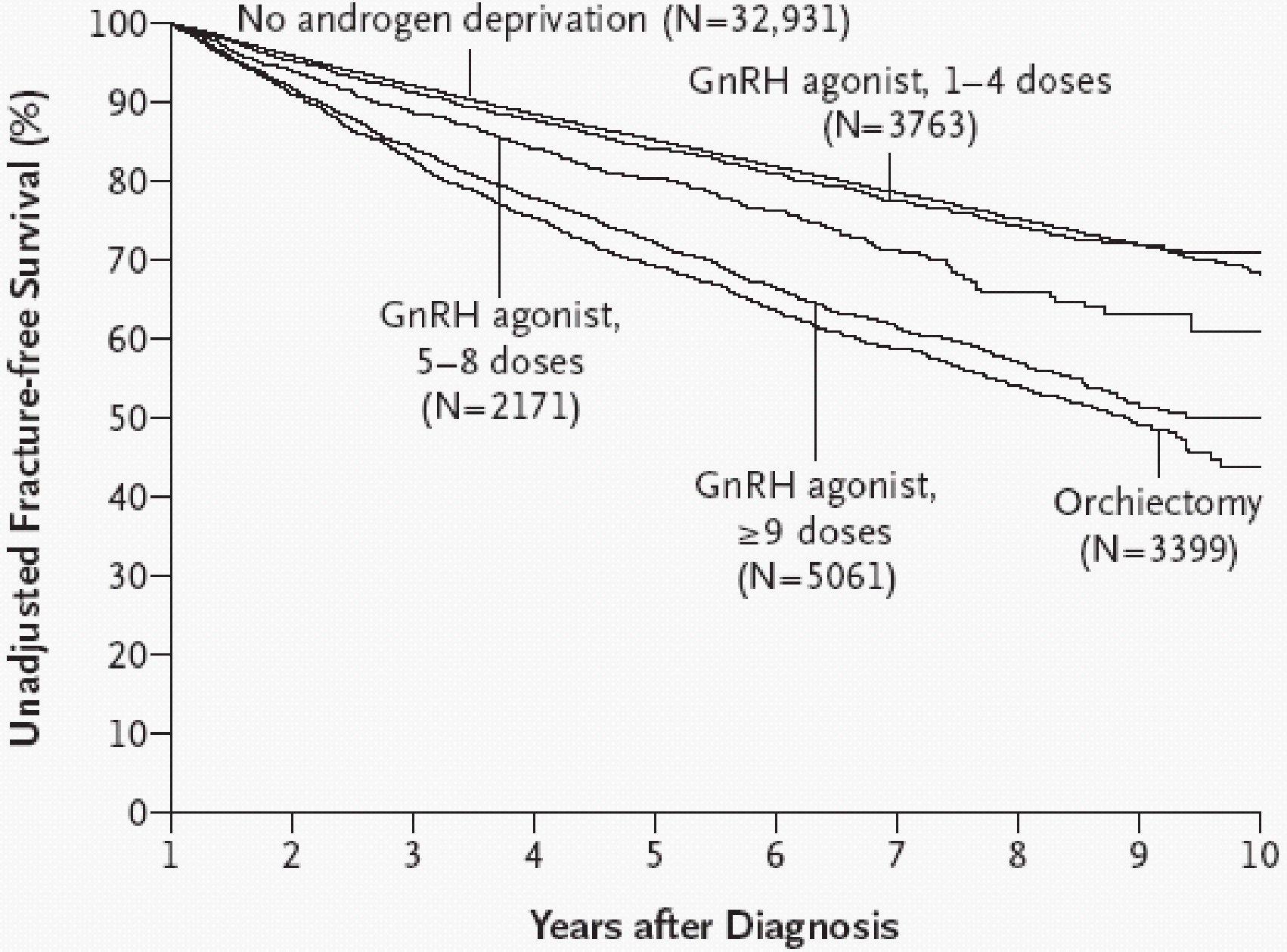
† Clinical progression was defined by increasing symptoms of bone metastases; progression according to the Response Evaluation Criteria in Solid Tumors, version 1.0; or clinical deterioration due to cancer according to the investigator's opinion.

Sweeney CJ et al. N Engl J Med 2015;373:737-746

What are the Side Effects of ADT?

Side-Effects of ADT

"Big Three"	What you see	What you don't see	What you feel
Loss of libido	Weight gain	Loss of BMD	Fatigue, Lack of energy, Lack of initiative
Erectile dysfunction	Gynecomastia	Anemia	Depression
Hot flashes	Loss muscle mass, strength	Onset/worsening of lipids, HTN, diabetes, CVD	Emotional lability
	Decr size penis and testes		Cognitive function
	Hair changes		


No androgen deprivation (N=32,931)
GnRH agonist, 1–4 doses (N=3763)
GnRH agonist, 5–8 doses (N=2171)
GnRH agonist, ≥9 doses (N=5061)
Orchiectomy (N=3399)
Unadjusted Fracture-free Survival (%)
100
90
80
70
60
50
40
30
20
10
0
1
2
3
4
5
6
7
8
9
10
Years after Diagnosis

Prevention of Fractures from ADT

- Replete Vitamin D
- Adequate calcium intake
- Risk of fracture assessment based on health profile
- Baseline and yearly BMD

N= 16,888
ADT 2,397 + no ADT 14,491

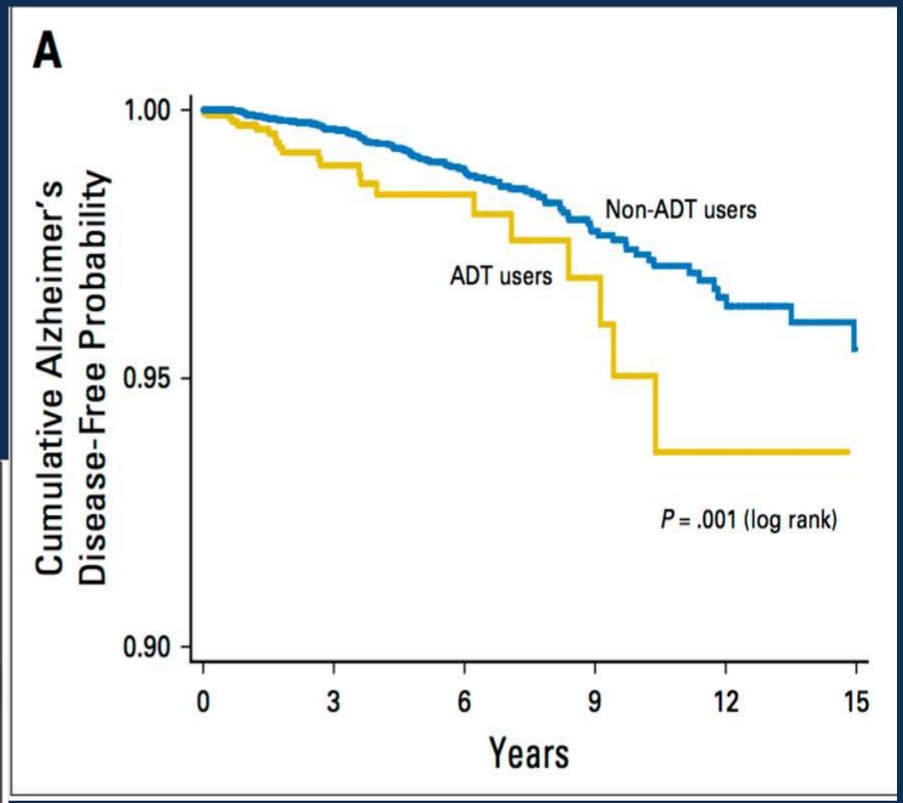
ADT and alzheimer's

Table 3. Propensity Score–Matched Cox Regression Analysis for the Association of ADT Use With Alzheimer's Disease

Exposure	HR (95% CI)	*P*
Propensity score–matched analysis		
No ADT use	Ref	Ref
ADT use	1.88 (1.10 to 3.20)	.021
Traditional multivariable-adjusted analysis		
No ADT use	Ref	Ref
ADT use	1.66 (1.05 to 2.64)	.031

Table 4. Propensity Score–Matched Cox Regression Analysis for the Association of ADT Use With Alzheimer's Disease by Therapy Duration

Duration of ADT Use (Months)	HR (95% CI)	*P*	*P* for Trend*
No ADT use	Ref	Ref	.016
ADT users			
< 12 months ADT use	1.62 (0.82 to 3.21)	.165	
≥ 12 months ADT use	2.12 (1.11 to 4.03)	.011	



Nead KT, et al. **J Clin Oncol**. 2015 Dec 7

Castrate Resistant Prostate Cancer (CRPC)

- Definition: Rising PSA or objective progression (bone +/- soft tissue) despite castrate testosterone levels
  - Serum Testosterone < 50ng/dl or < 1.7nM/dl
- CRPC will develop in all patients who receive Androgen Deprivation Therapy
- Androgen Receptor (AR) is still present and functional

Castrate Resistant Prostate Cancer

- Increased Androgen Biosynthesis
  - Persistent androgens in primary tumors[1,2]
  - Persistent androgens in metastasis[3]
  - Upregulated enzymes of steroidogenesis[3]

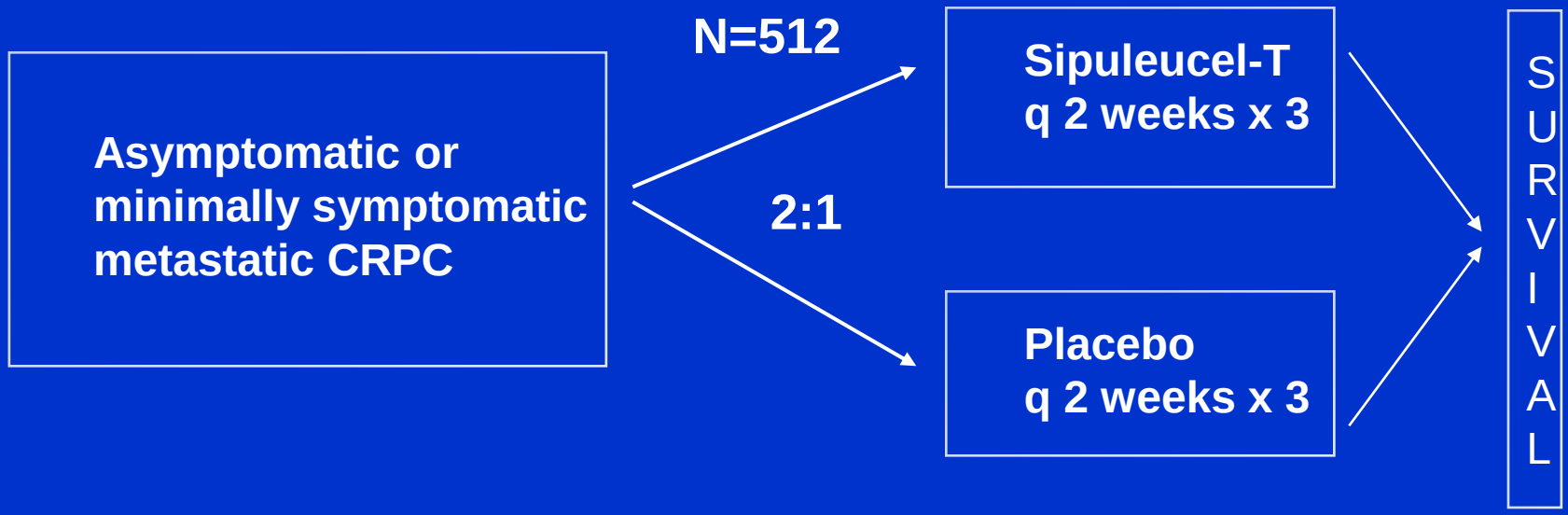
- Persistent Androgen Receptor Signaling
  - AR amplification
  - AR splice variants
  - AR signaling via alternate ligands (steroid receptor superfamily)
  - AR signaling via PI3Kinase/ MAPKinase etc

1. Geller J, 1969.
2. Mohler JL et al. *Clin Cancer Res*. 2004;10:440-448.
3. Montgomery RB et al. *Cancer Res*. 2008; 68:4447-4454.
4. Ryan C et al. 2008 ASCO:5018.
5. Scher HI et al. 2008 ASCO:5006.

Castration Resistant Prostate Cancer- New Clinical Insights

- Most men with CRPC do not yet have radiographic metastases
- Median time to metastasis is 2-3 years
- Determinants of time to onset of metastases are level of PSA and PSADT

Randomized Phase 3 IMPACT Trial



Primary endpoint: Overall survival

Secondary endpoint: Objective disease progression

Kantoff PW, et al, NEJM, July, 2010

IMPACT Study

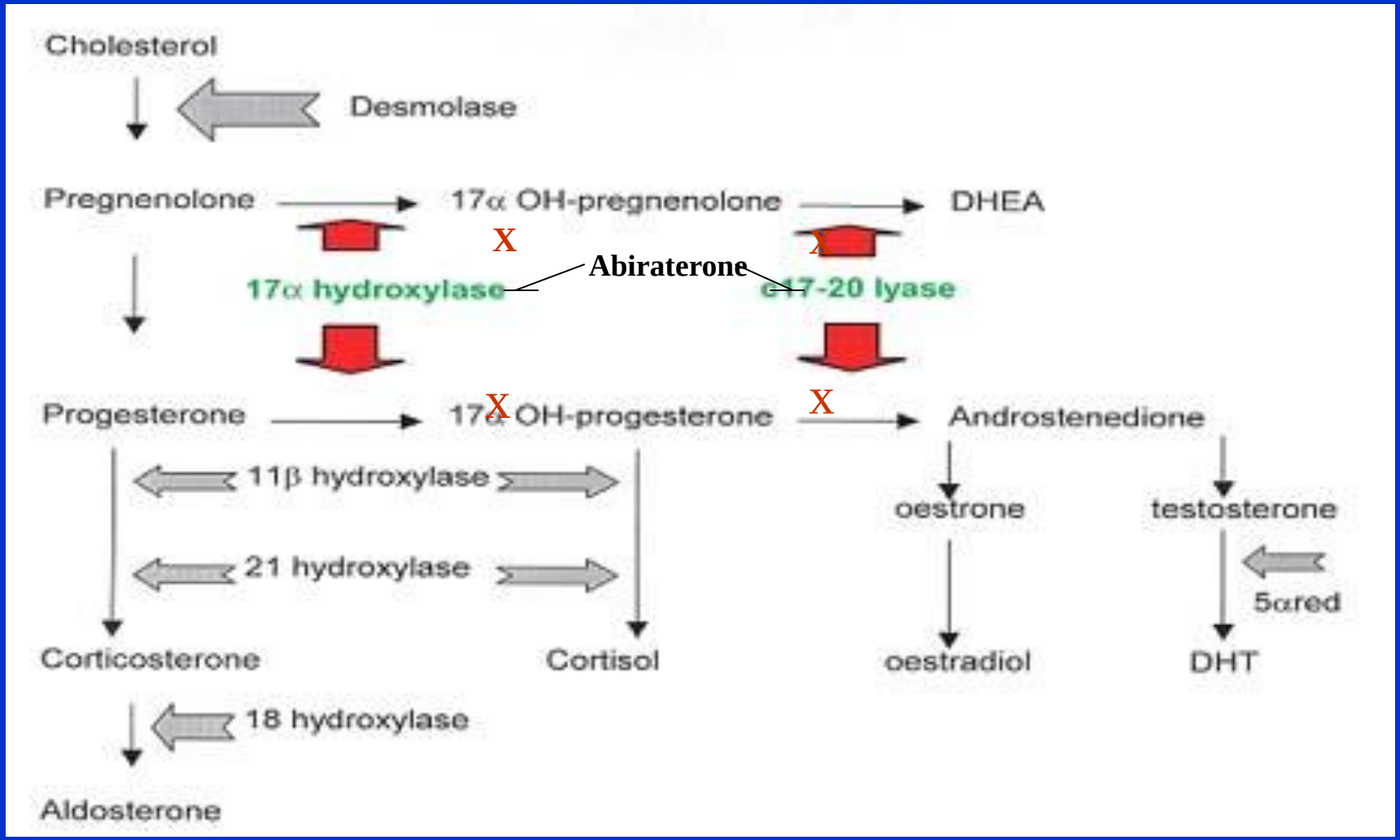
- PROVENGE improved median survival by 4.1 months compared to the control group (25.8 months versus 21.7 months). Overall, PROVENGE reduced the risk of death by 22.5%
- No effect on the time to disease progression was observed
- No evidence of a favorable effect on PSA, tumor regression, or stabilization of soft tissue or bony disease radiographically, or health-related quality of life

Kantoff PW, et al, NEJM July, 2010

Novel Hormonal Agents

- Abiraterone - CYP 17 inhibitors
- Enzalutamide - Antiandrogen

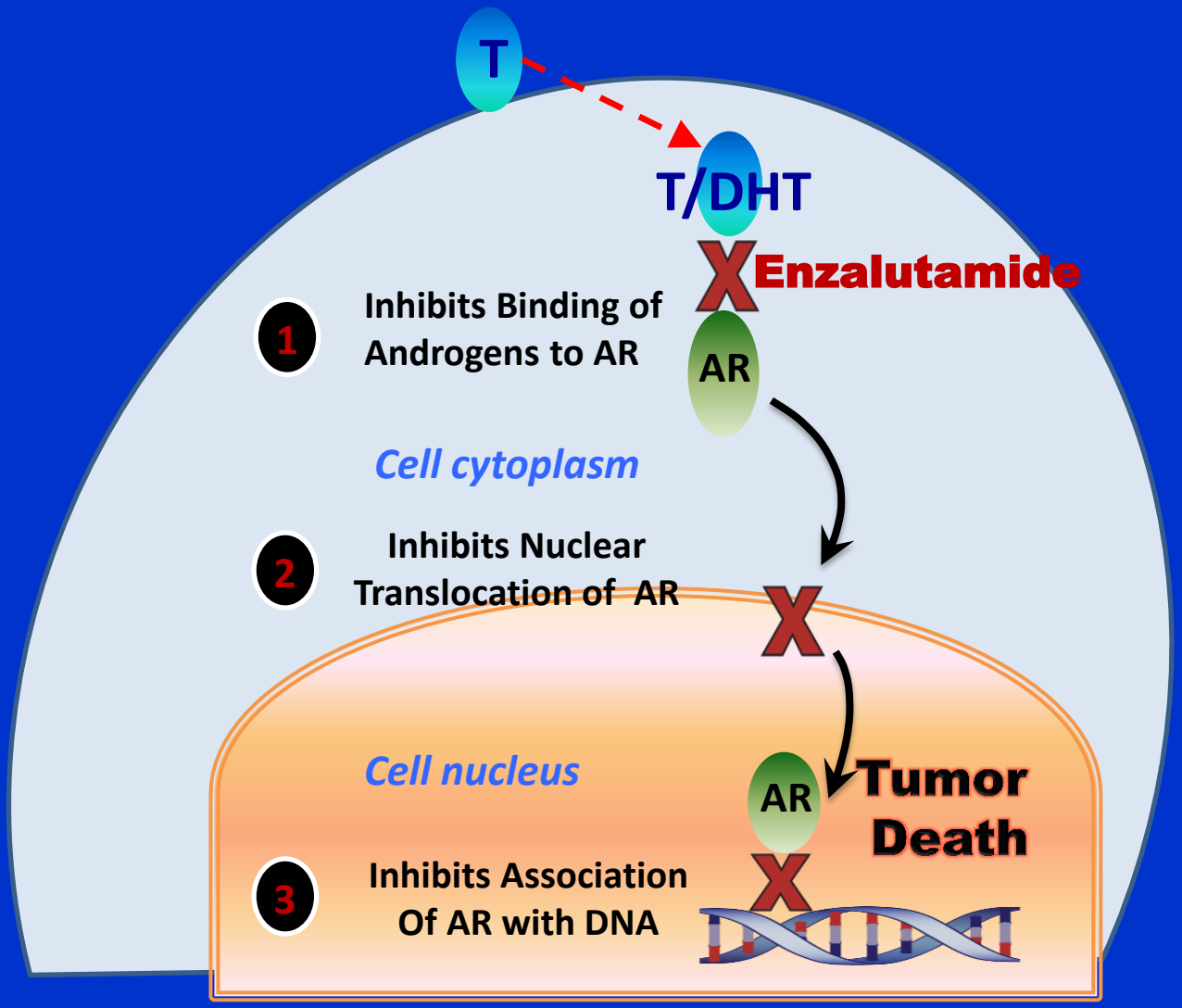
Abiraterone Acetate
17α hydroxylase, c17-20 lyase inhibitor



Reid AH, et al. Significant and sustained antitumor activity in post-docetaxel, CRPC with CYP17 inhibitor abiraterone acetate. J Clin Onc 2010;28:1489-95.

Enzalutamide (MDV3100)

- Oral investigational drug rationally designed to target AR signaling, impacting multiple steps in AR signaling pathway
- No demonstrated agonist effects in pre-clinical models



Tran et al. Science 2009;324:787–90.

CRPC therapies that offer a survival benefit

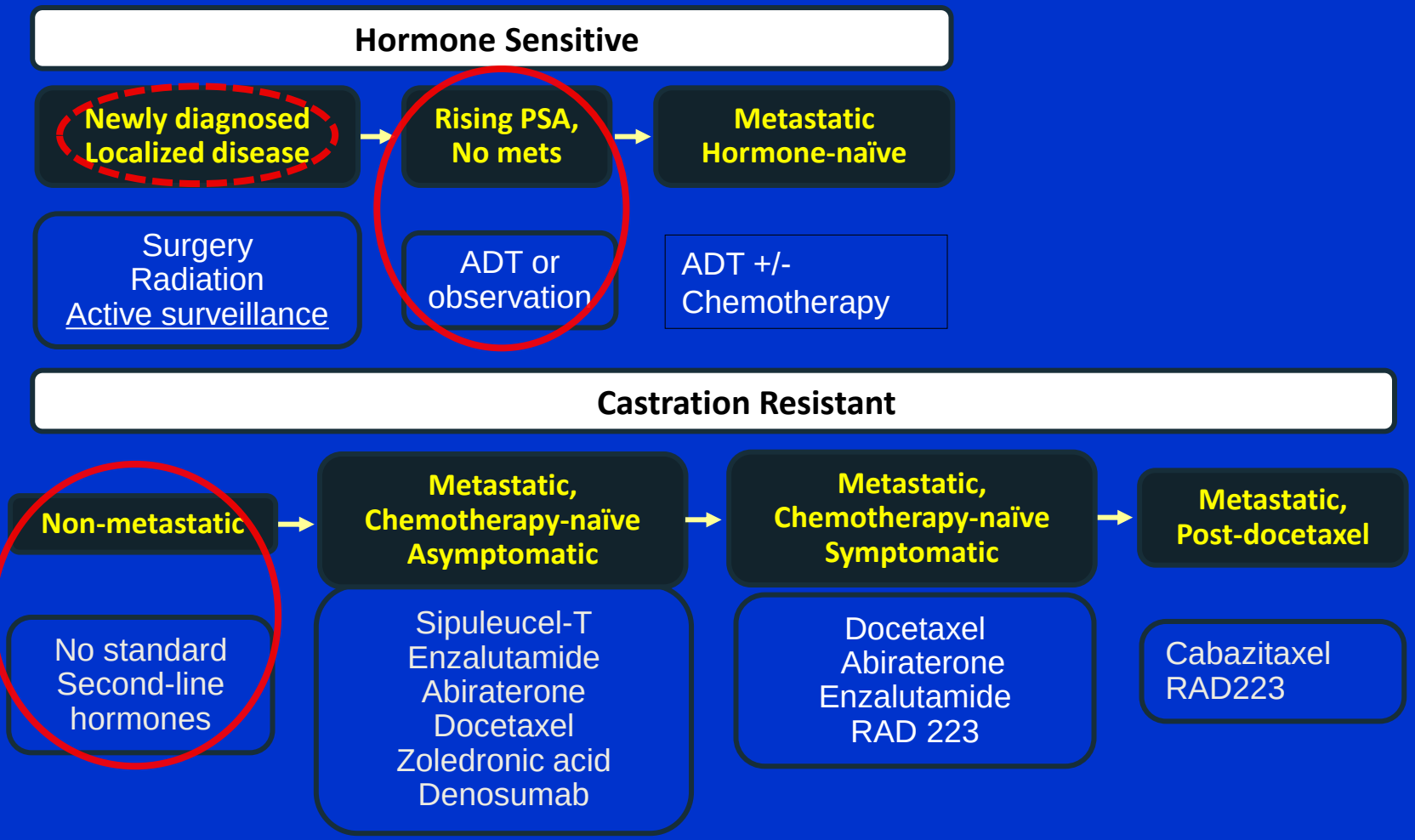
Year approved	Agent	Indication	PFS benefit	OS benefit
2004	Docetaxel	mCRCP	?	√
2010	Sipuleucel-T	a - or minimally symptomatic mCRPC	No	√
2010	Cabazitaxel	Post-docetaxel mCRPC	√	√
2011 and 2012	Abiraterone	mCRPC	√	√
2012 and 2014	Enzalutamide	mCRPC	√	√
2013	Radium-223	Symptomatic bone predominant mCRCP	SSRE	√

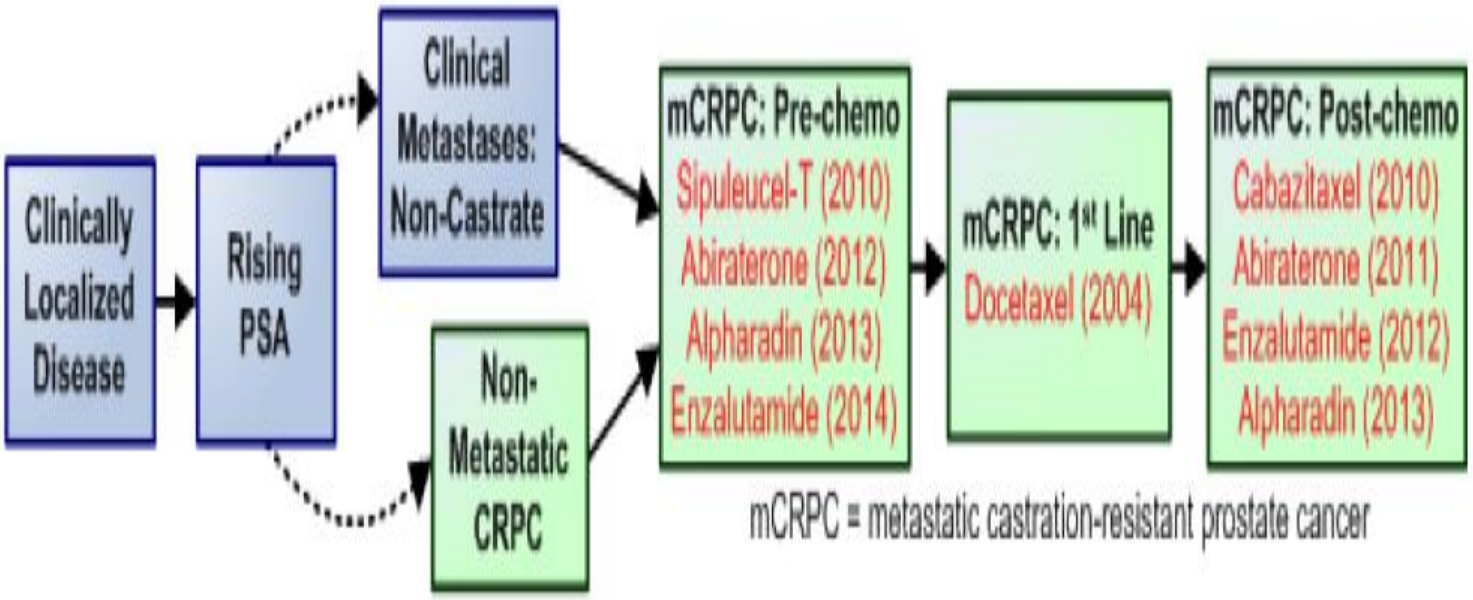
OS Benefit in Recent CRPC Trials

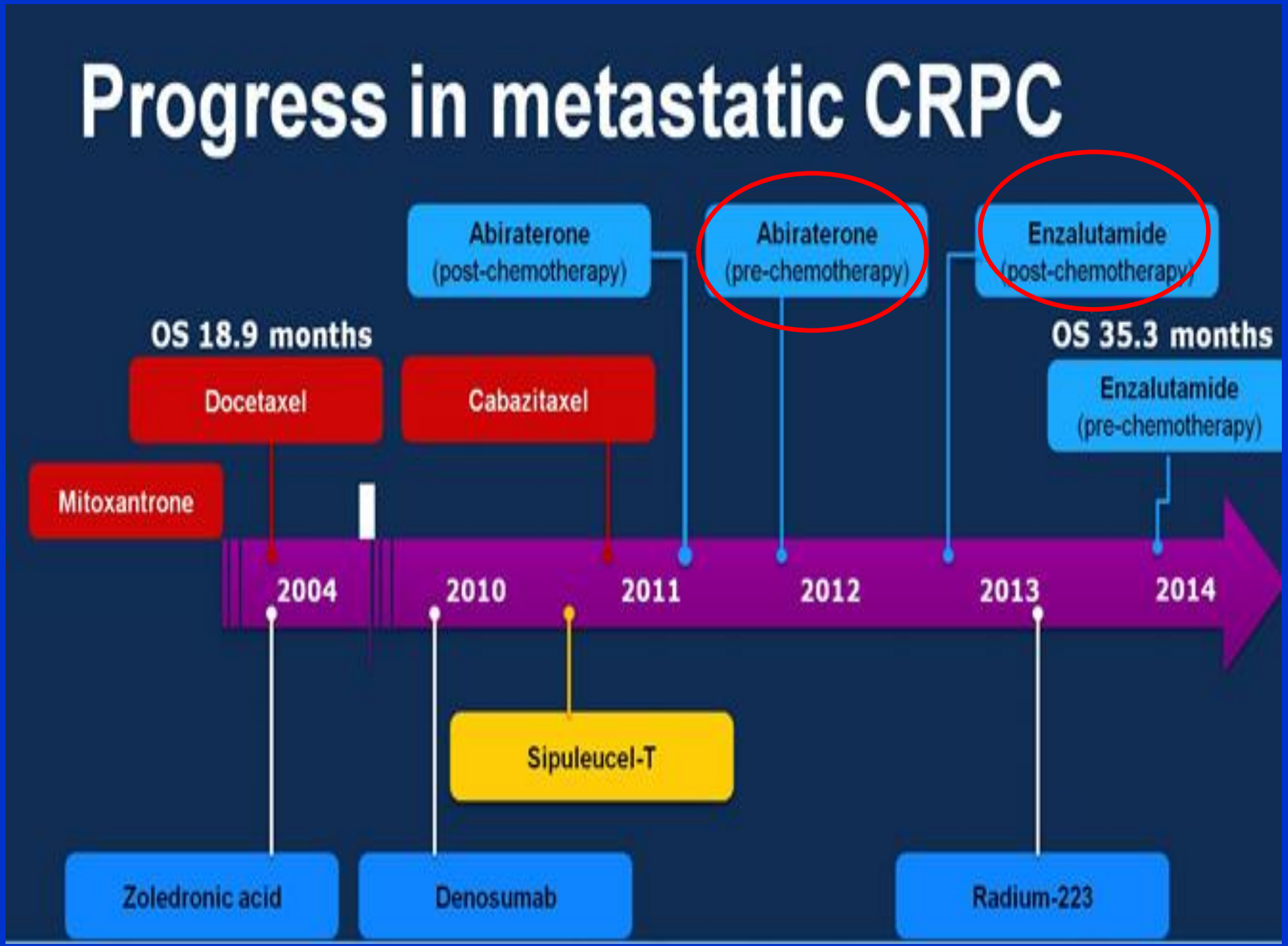
Trial/ Agent	Mechanism	Comparator	Survival (months)	Hazard Ratio	P-value	Reference
AFFIRM Enzalutamide	Androgen Receptor Signaling Inhibitor	Placebo	18.4 vs. 13.6	0.631	<0.0001	de Bono et al, ASCO 2012
COU-AA-301 Abiraterone + prednisone	CYP17 Inhibitor	Placebo + prednisone	14.8 vs. 10.9	0.646	<0.0001	de Bono et al, NEJM 2011
TROPIC Cabazitaxel + prednisone	Cytotoxic	Mitoxantrone + prednisone	15.1 vs. 12.7	0.70	<0.0001	de Bono et al, Lancet 2010
Radium 223*	Alpha-particle emitting radionuclide	Placebo	14.9 vs 11.3	0.69	0.0018	Parker et al, ESMO 2011

**** Only 60% of these patients were post-docetaxel patients***

Prostate Cancer Landscape: 2017



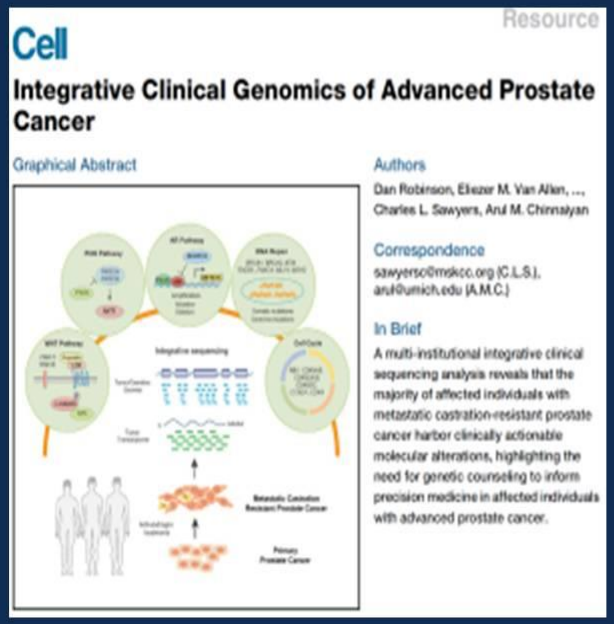

Clinically Localized Disease
Rising PSA
Clinical Metastases: Non-Castrate
Non-Metastatic CRPC
mCRPC: Pre-chemo
Sipuleucel-T (2010)
Abiraterone (2012)
Alpharadin (2013)
Enzalutamide (2014)
mCRPC: 1st Line
Docetaxel (2004)
mCRPC: Post-chemo
Cabazitaxel (2010)
Abiraterone (2011)
Enzalutamide (2012)
Alpharadin (2013)
mCRPC = metastatic castration-resistant prostate cancer


Progress in metastatic CRPC
Abiraterone (post-chemotherapy)
Abiraterone (pre-chemotherapy)
Enzalutamide (post-chemotherapy)
OS 18.9 months
OS 35.3 months
Docetaxel
Cabazitaxel
Enzalutamide (pre-chemotherapy)
Mitoxantrone
2004
2010
2011
2012
2013
2014
Sipuleucel-T
Zoledronic acid
Denosumab
Radium-223

2 Major Milestones in 2015

Genetic Blueprint of Prostate Cancer

SU2C



Cell

Resource

Integrative Clinical Genomics of Advanced Prostate Cancer

Graphical Abstract

Authors

Dan Robinson, Eliezer M. Van Allen, ..., Charles L. Sawyers, Arul M. Chinnaiyan

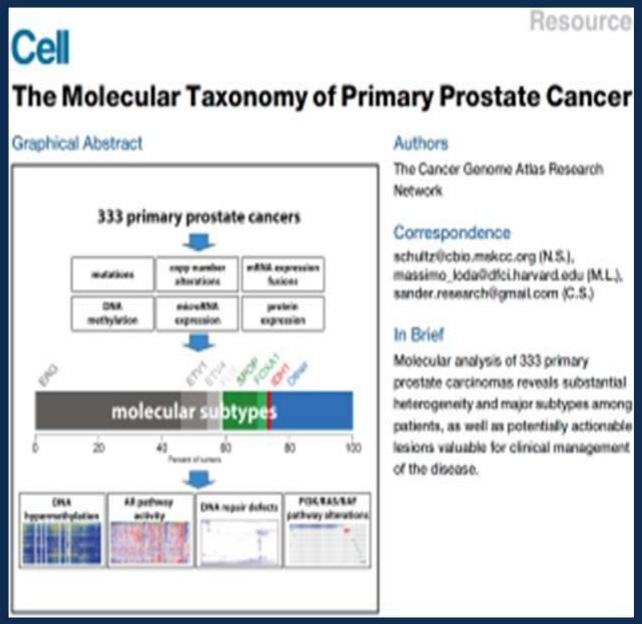
Correspondence

sawyersc@mskcc.org (C.L.S.), arul@umich.edu (A.M.C.)

In Brief

A multi-institutional integrative clinical sequencing analysis reveals that the majority of affected individuals with metastatic castration-resistant prostate cancer harbor clinically actionable molecular alterations, highlighting the need for genetic counseling to inform precision medicine in affected individuals with advanced prostate cancer.

TCGA



Cell

Resource

The Molecular Taxonomy of Primary Prostate Cancer

Graphical Abstract

333 primary prostate cancers

molecular subtypes

Authors

The Cancer Genome Atlas Research Network

Correspondence

schultz@cbio.mskcc.org (N.S.), massimo_loda@dfci.harvard.edu (M.L.), sander.research@gmail.com (C.S.)

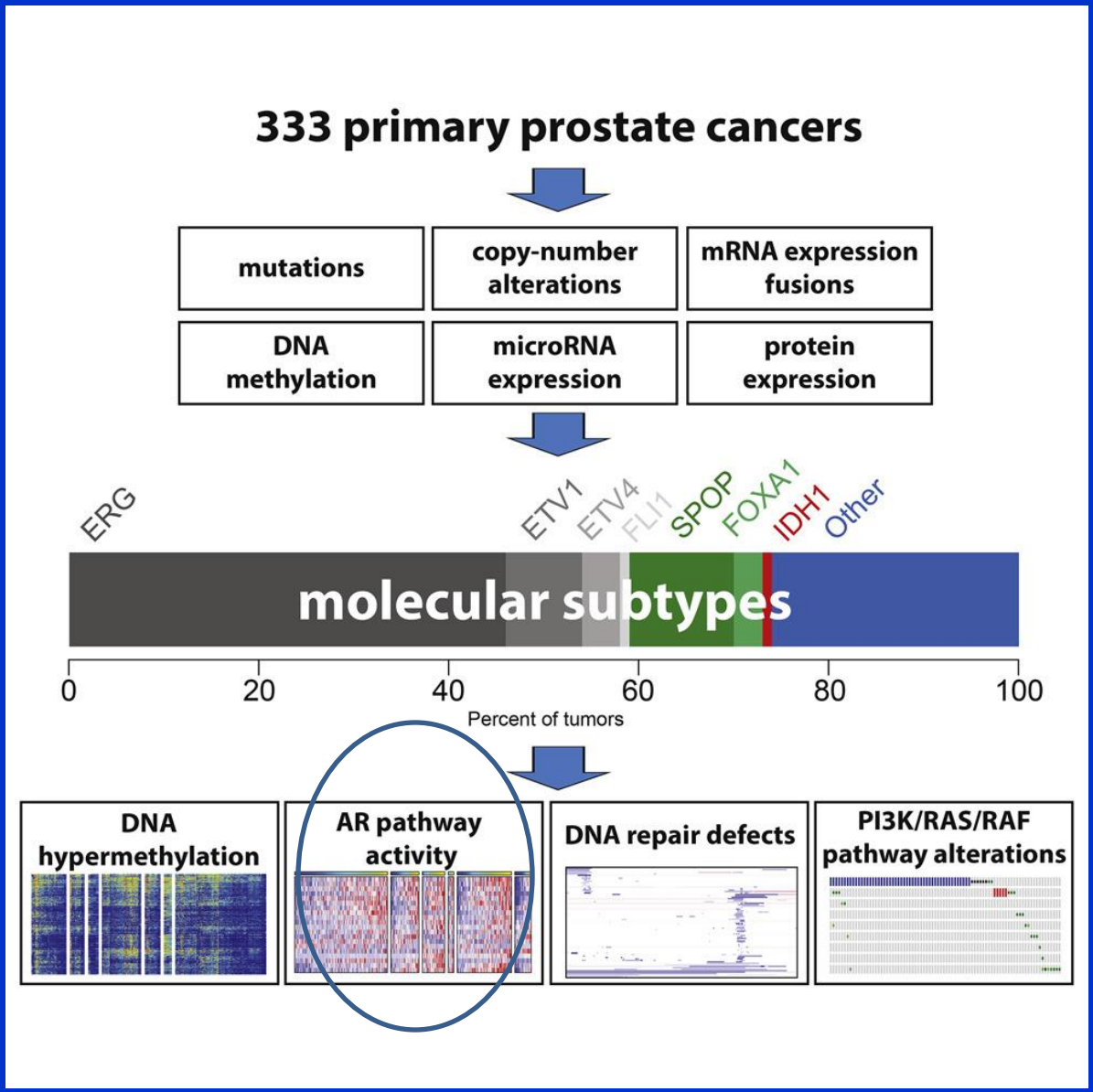
In Brief

Molecular analysis of 333 primary prostate carcinomas reveals substantial heterogeneity and major subtypes among patients, as well as potentially actionable lesions valuable for clinical management of the disease.

A clearer view of targets for therapy

PRESENTED AT: **2016 Genitourinary Cancers Symposium**

Presented by: Nima Sharifi, M.D.



Cell 2015 163, 1011-1025DOI: (10.1016/j.cell.2015.10.025)

333 primary prostate carcinomas – 74% associated with a molecular abnormality

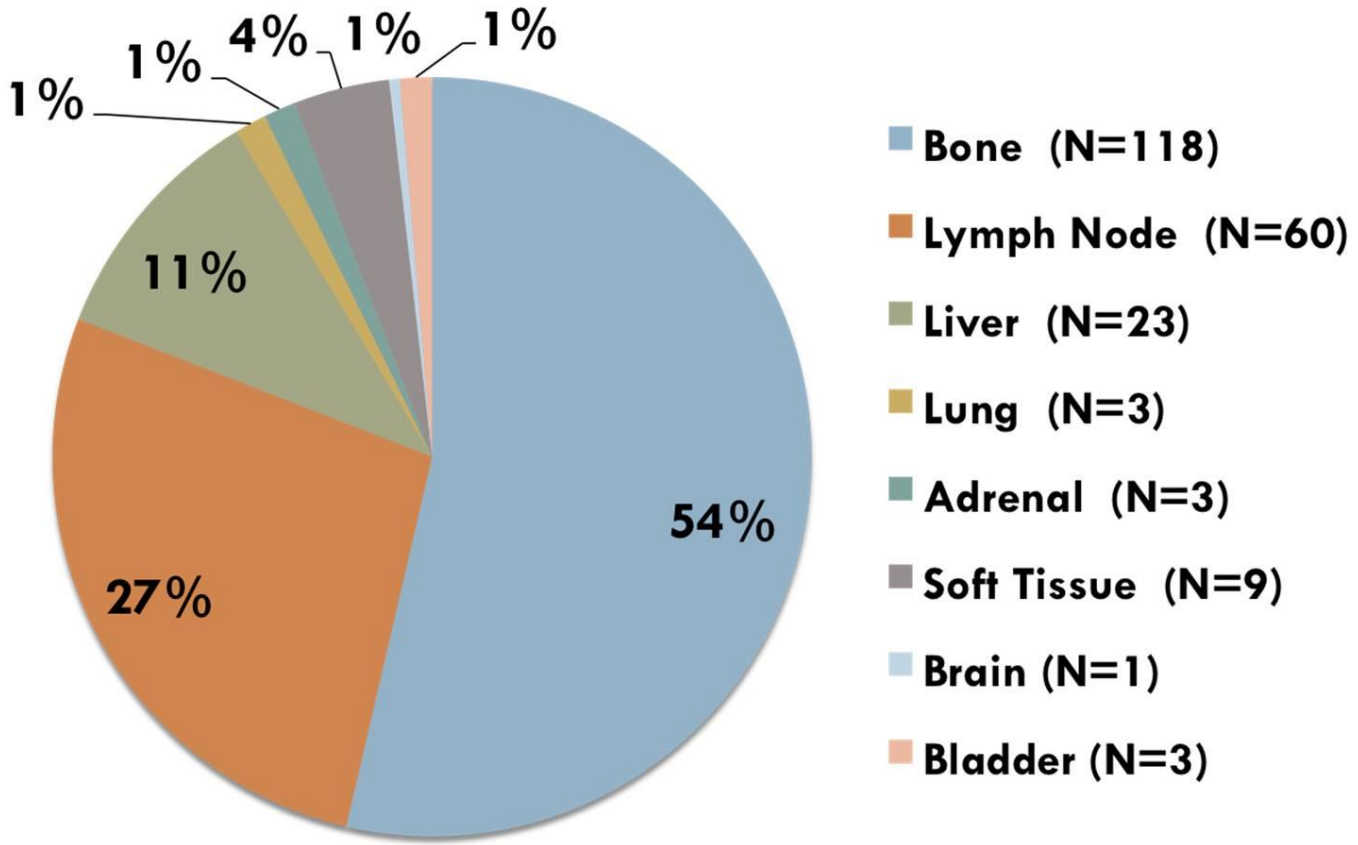
Seven subtypes defined by ETS fusions or mutations in SPOP, FOXA1, and IDH1

Substantial epigenetic heterogeneity, including a hypermethylated IDH1 mutant subset

Presumed actionable lesions in the PI3K, MAPK, and DNA repair pathways

Sites of Biopsy Acquisition

(as of 12/1/15; n = 220)

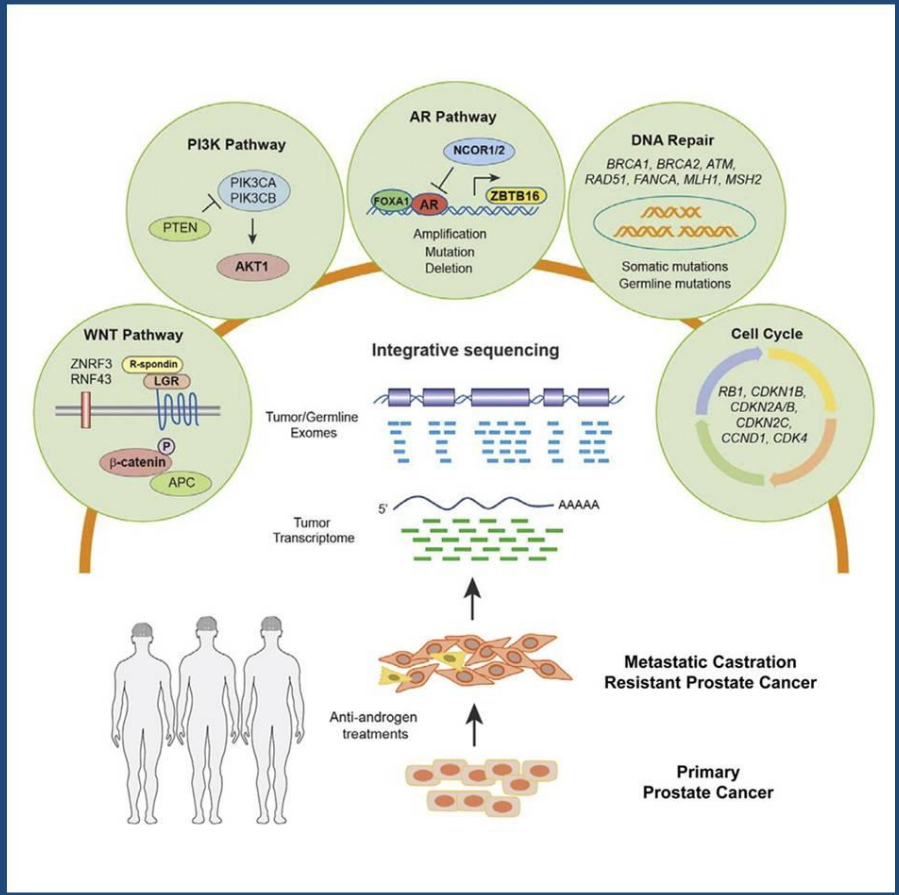


KNIGHT CANCER INSTITUTE
Oregon Health & Science University

Histology of 124 Evaluable Biopsies

- 13% classic small cell/neuroendocrine cancer (SCNC)
- 26% of biopsies are an Intermediate Atypical Carcinoma (IAC) distinct from AdenoCa and SCNC
- 26% of biopsies had distinct, but mixed populations

Identifying Molecular Alterations in CRPC



Robinson *et. al.* Cell 161, 1215-1228 (2015)

KNIGHT CANCER INSTITUTE
Oregon Health & Science University

N ENGL J MED 375;5 NEJM.ORG AUGUST 4, 2016

The New England Journal of Medicine

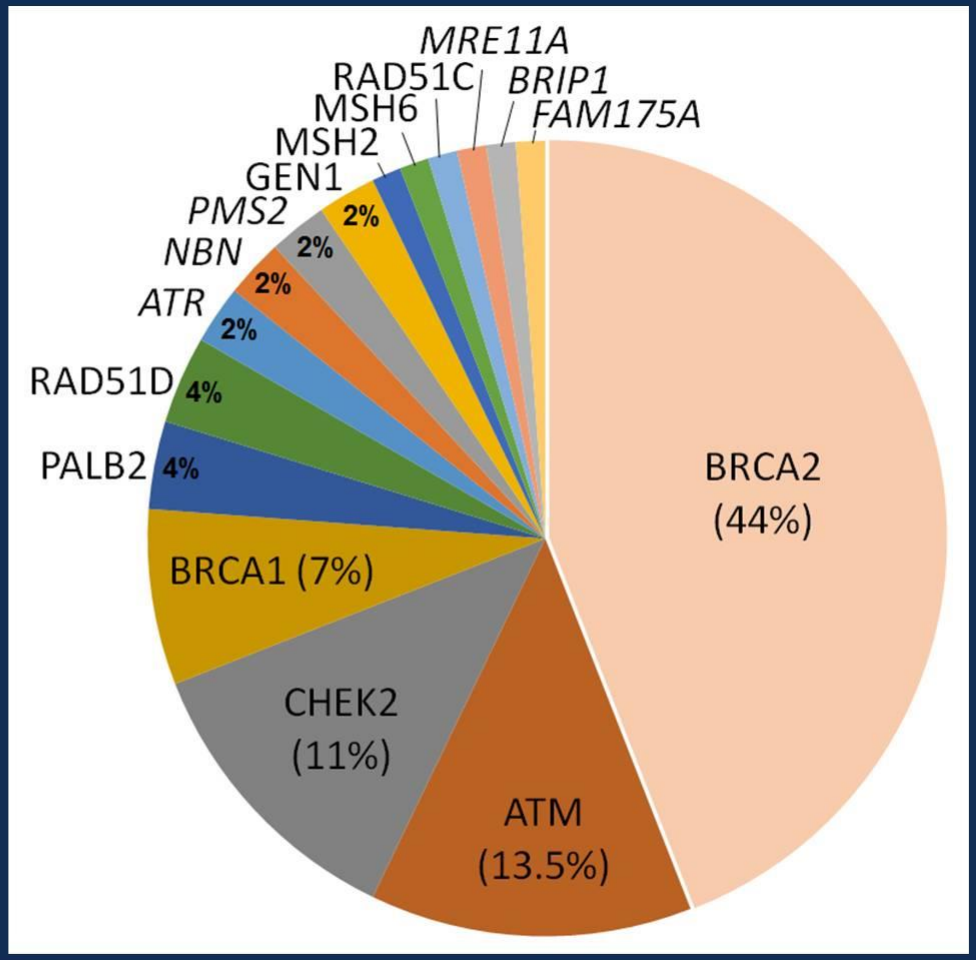
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

C.C. Pritchard, J. Mateo, M.F. Walsh, N. De Sarkar, W. Abida, H. Beltran, A. Garofalo, R. Gulati, S. Carreira, R. Eeles, O. Elemento, M.A. Rubin, D. Robinson, R. Lonigro, M. Hussain, A. Chinnaiyan, J. Vinson, J. Filipenko, L. Garraway, M.-E. Taplin, S. AlDubayan, G.C. Han, M. Beightol, C. Morrissey, B. Nghiem, H.H. Cheng, B. Montgomery, T. Walsh, S. Casadei, M. Berger, L. Zhang, A. Zehir, J. Vijai, H.I. Scher, C. Sawyers, N. Schultz, P.W. Kantoff, D. Solit, M. Robson, E.M. Van Allen, K. Offit, J. de Bono, and P.S. Nelson

RESULTS



RESULTS

Case Series	n	Mutated	%
SU2C/PCF Discovery	150	15	10.0%
SU2C/PCF Validation	84	9	10.7%
MSKCC	124	23	18.5%
Royal Marsden	131	16	12.2%
University of Washington	91	8	8.8%
Weill Cornell	69	7	10.1%
University of Michigan	43	4	9.3%
Combined	**692**	**82**	**11.8%**

Biomarker based treatment

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 29, 2015 VOL. 373 NO. 18

DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

J. Mateo, S. Carreira, S. Sandhu, S. Miranda, H. Mossop, R. Perez-Lopez, D. Nava Rodrigues, D. Robinson, A. Omlin, N. Tunariu, G. Boysen, N. Porta, P. Flohr, A. Gillman, I. Figueiredo, C. Paulding, G. Seed, S. Jain, C. Ralph, A. Protheroe, S. Hussain, R. Jones, T. Elliott, U. McGovern, D. Bianchini, J. Goodall, Z. Zafeiriou, C.T. Williamson, R. Ferraldeschi, R. Riisnaes, B. Ebbs, G. Fowler, D. Roda, W. Yuan, Y.-M. Wu, X. Cao, R. Brough, H. Pemberton, R. A'Hern, A. Swain, L.P. Kunju, R. Eeles, G. Attard, C.J. Lord, A. Ashworth, M.A. Rubin, K.E. Knudsen, F.Y. Feng, A.M. Chinnaiyan, E. Hall, and J.S. de Bono