Prostate Cancer: Early and Locally Advanced Disease

Daniel P Petrylak MD
Professor of medicine and Urology
Smilow Cancer Center
Yale University School of Medicine

Prostate Cancer 2024

- Leading male US cancer, 2nd cancer deaths (lung #1)
- New: 174,650 Deaths: 31, 620
- Prevelance of metastatic disease: 100,000
- Lifetime US risk:

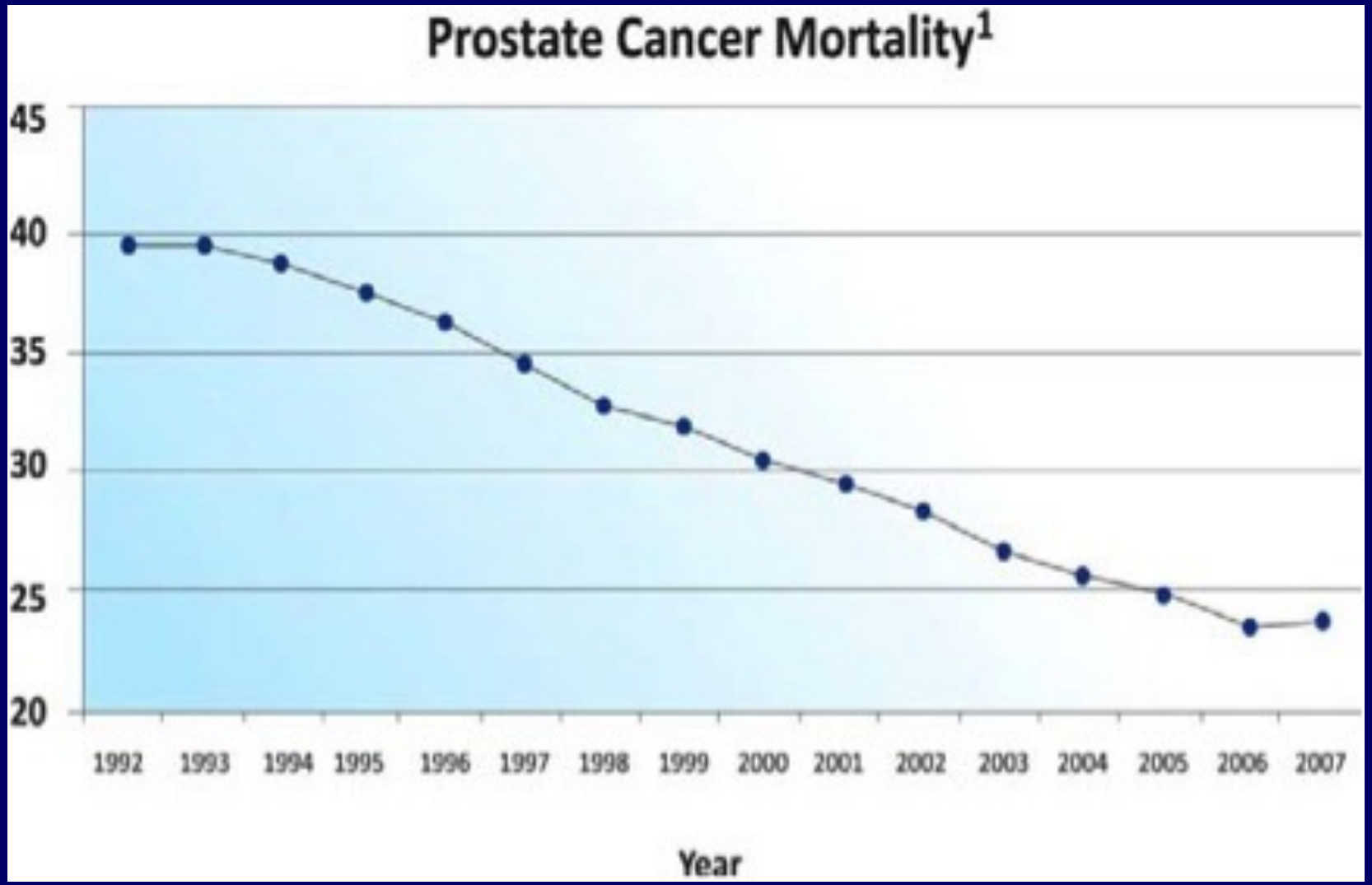
  Diagnosis: ~17% Death: ~3%
- Every 2 Minutes an American is diagnosed with prostate cancer and every 18 Minutes an American dies of prostate cancer
- Since 2014,the incidence rate has increased by 3% per year overall and by about 5% per year for advanced-stage prostate cancer.

CA CANCER J CLIN
20324

Impact of PSA Testing on Clinical Stage at Diagnosis

Stage	1990	2009
Localized disease	68%	→ 91%
Metastases to bone	21% 1 out of 5	→ 4% 1 out of 25

Courtesy Dr. Patrick Walsh



Death rates per 100,000 US Men (SEER /NCI Data)

Why a Reduction in Prostate Cancer Mortality?

- Better therapy (radiation, surgery)
- Earlier use of hormonal therapy
- Changes in cause of death assignment
- Other
  - Lifestyle changes
  - Medication use (statins / cox-2 inhibitors)
- Early detection / screening?

Screening for Prostate Cancer: U.S. Preventive Services Task Force Recommendation Statement

Virginia A. Moyer, MD, PhD, on behalf of the U.S. Preventive Services Task Force*

Description: Update of the 2008 U.S. Preventive Services Task Force (USPSTF) recommendation statement on screening for prostate cancer.

Methods: The USPSTF reviewed new evidence on the benefits and harms of prostate-specific antigen (PSA)--based screening for prostate cancer, as well as the benefits and harms of treatment of localized prostate cancer.

Recommendation: The USPSTF recommends against PSA-based screening for prostate cancer (grade D recommendation).

This recommendation applies to men in the general U.S. population, regardless of age. This

Moyer VA; U.S. Preventive Services Task Force.Ann Intern Med. 2012 Jul 17;157(2):120-34

USPSTF

- What they did that was good:
  - Stimulated renewed dialogue
  - Fine print: discuss screening with your provider!
  - Fine print: maybe screen less often with low PSA!
- Where they did not get it:
  - Excess focus on complications
  - Population vs. individual w/risk factors
  - Treatment impact on survival
  - Benefits of PSA detected cancer
  - Increasing use of active surveillance

Prostate Cancer "Screening" Trials

- Norrköping
- Quebec Study (RCT) – 1998
- Swedish Study (RCT) – 2004

Deviations / limitations In statistical methods

- Tyrol Study – Population comparison (+ screen effect)
- PLCO
- ERSP
- Göteborg

Intent to treat, data and safety monitoring, scientific rigor, competent researchers (Reported 2009,2010)

- CAP and ProtecT (UK) are ongoing

Two Conflicting Studies: Published Together

PLCO: No reduction in PCa mortality (76,000 USA)

- Large number pre-screened; Contaminated control group
- Limited follow up; Single cut point for PSA

ERSPC: 20% reduction in mortality (182,000 EU)
25% reduction in metastatic disease

- No DRE; Multiple countries, variable criteria (Included Göteborg)
- Deaths reduced after 8 yrs
- Need to screen 1440 and
- Treat 48 additional to prevent one PC death

PLCO: Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial
ERSPC: European Randomized Study of Screening for Prostate Cancer

Andriole G, et al. *N Engl J Med*. 2009;360:1310-1319.
Schröder F, et al. *N Engl J Med*. 2009;360:1320-1328.

ERSPC Year 13 Follow Up

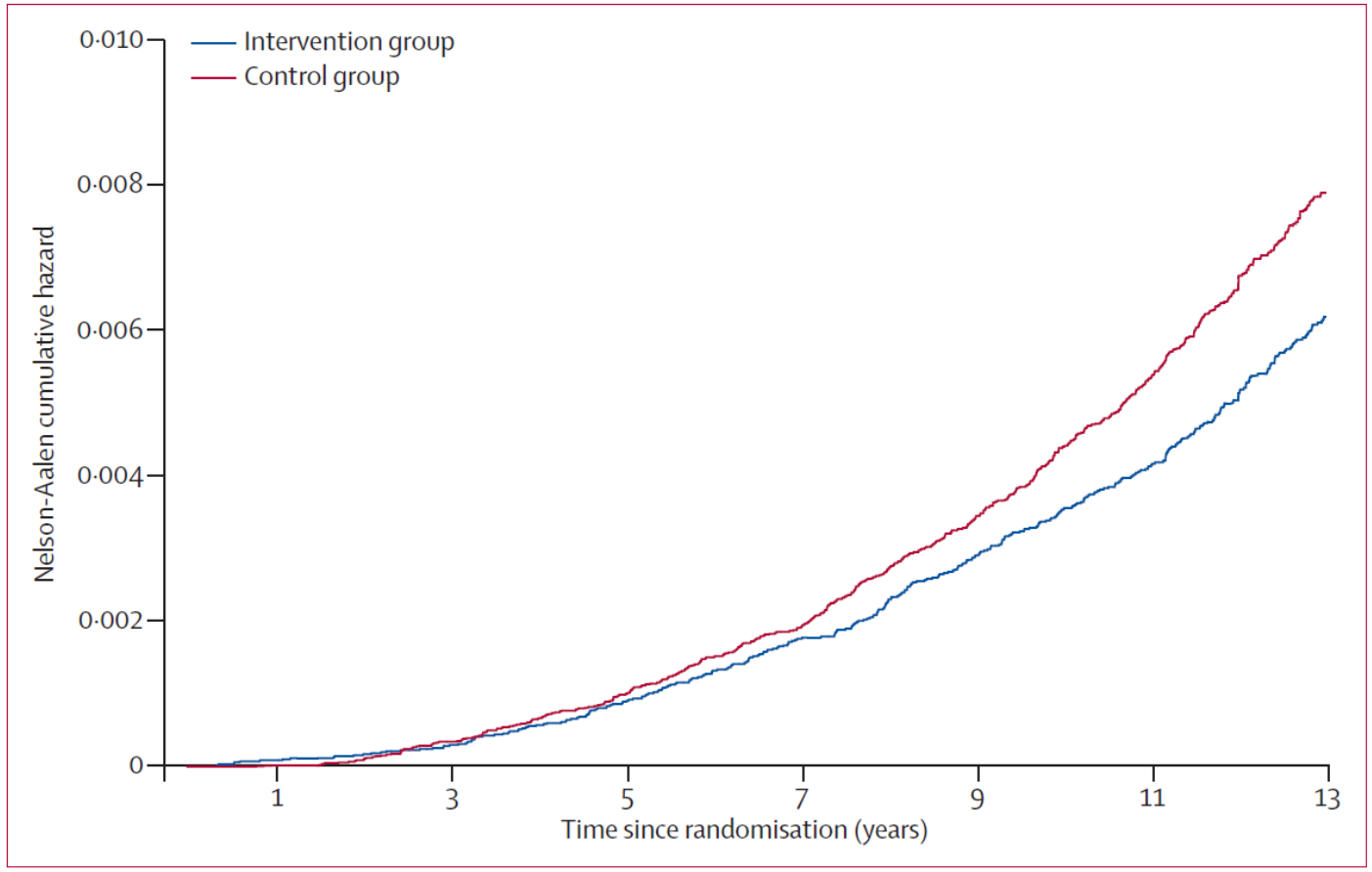


Figure 2: **Nelson–Aalen estimates of cumulative prostate cancer mortality (all centres, excluding France)**

NNT has fallen from 35 to 27 at 13 years

Schroder, et al. Lancet Volume 384, No. 9959, p2027–2035, 6 December 2014

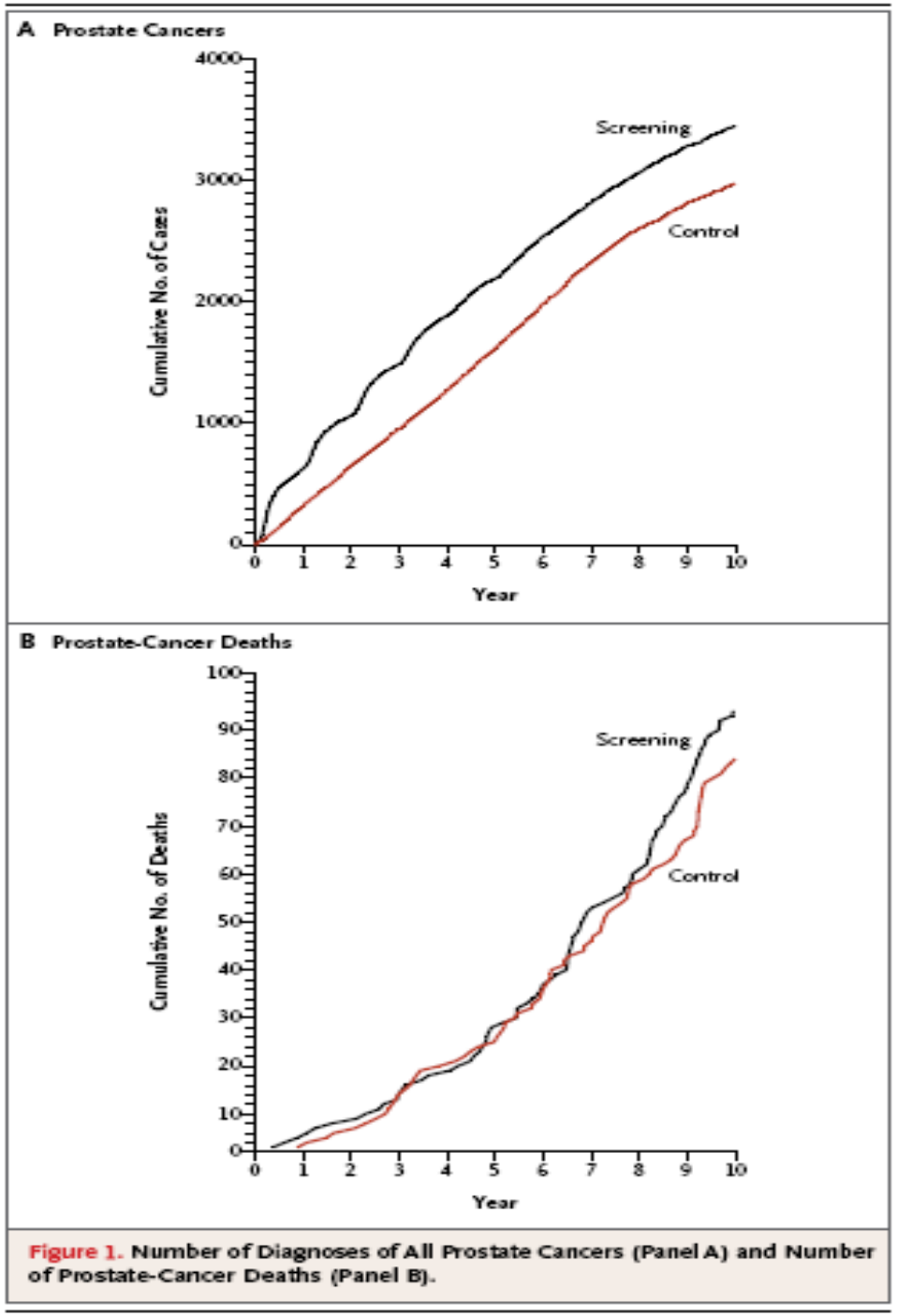


Figure 1. Number of Diagnoses of All Prostate Cancers (Panel A) and Number of Prostate-Cancer Deaths (Panel B).

PLCO Trial suggested that PSA screening increases cancer detection but does not decrease risk of death

Andriole et al. NEJM 360:1310, 2009

PLCO Highly Flawed?

- Supposed to be a randomized trial of PSA screened versus unscreened men BUT
  - 85% of screened had a PSA; 52% of the non-screened had a PSA
  - 44% had a PSA prior to randomization
- Risk of PC death ↓ by 25% with 2 or more PSAs vs no PSA
  - Similar to ERSPC; All that was needed in PLCO was two PSAs to ↓ risk of prostate cancer death!
- Removing those with co-morbidities improved results (Crawford, JCO 2010)
- Like ERSPC, many indolent cancers detected

Current PSA Screening Practice

- We have been screening too late in life
  - The clinically detected cancers in the 45-64 yo men for which active treatment was effective would likely have been screen detectable by PSA at least 5 years prior.
  - In the US randomized trial of active treatment (PIVOT) for screen-detected cancers, the mean age was 66.8 yrs; no overall mortality benefit observed.
    - BUT men with PSA>10 or aggressive features benefited

Drazer JCO May 1, 2011; Wilt NEJM 2012 Jul 19;367(3):203-13

PSA-Based Screening : What trials to date suggest

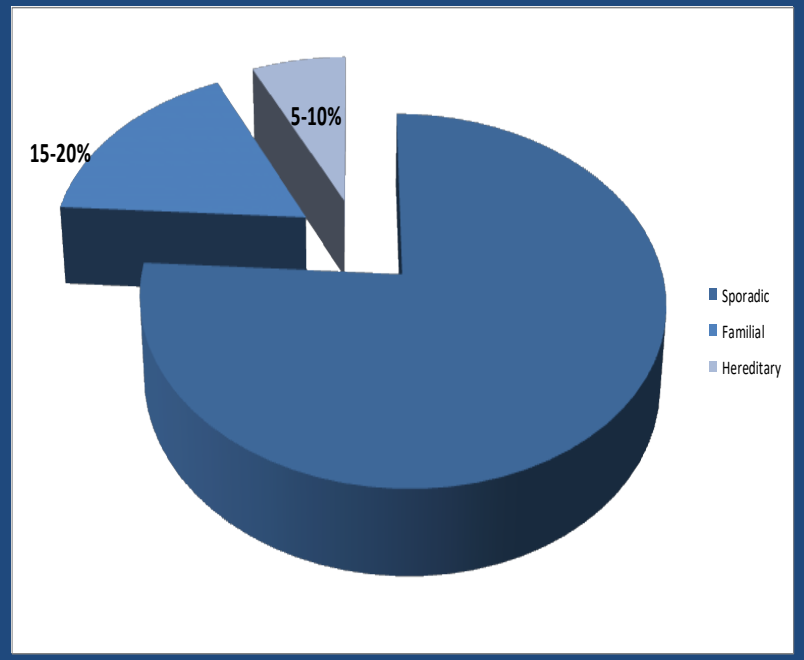
- Only makes sense in CERTAIN populations
  - Those at high risk for the disease
  - Those at high risk for death or morbidity from the disease
  - Those in good health with life expectancy > 10-15 yrs
- NOT FOR THE POPULATION AT LARGE
- Takes many years to see impact

Hereditary/Familial/Sporadic Cancer

- **Hereditary (5-10% of cases)**
  - Often due to a single inherited genetic mutation
  - Greatly **increases** lifetime risk
  - BRCA1, BRCA2, Lynch syndrome
  - HOXB13: Inherited prostate cancer

- **Familial (15-20% of cases)**
  - Some features of hereditary cancer
  - No detectable mutation identified
  - Possible genetic + environmental risk
  - Close family members increased risks

- **Sporadic (70-80% of cases)**
  - Exact cause unknown
  - No features of hereditary or familial cancers
  - No increased risks for close family members



Genetic Counseling for PCa Criterion

American College of Medical Genetics and Genomics (ACMG)

National Society of Genetic Counselors (NSGC)

Philadelphia Prostate Cancer Consensus 2017

NCCN 2018

- ≥ 2 cases of PCa age ≤55 in close relatives
- ≥ 3 FDRs with PCa
- Aggressive (Gl >7) PCa and ≥2 cases of breast, ovarian, and/or pancreatic cancer in close relative
- Metastatic prostate cancer
- Tumor sequencing w/mutations in hereditary cancer genes

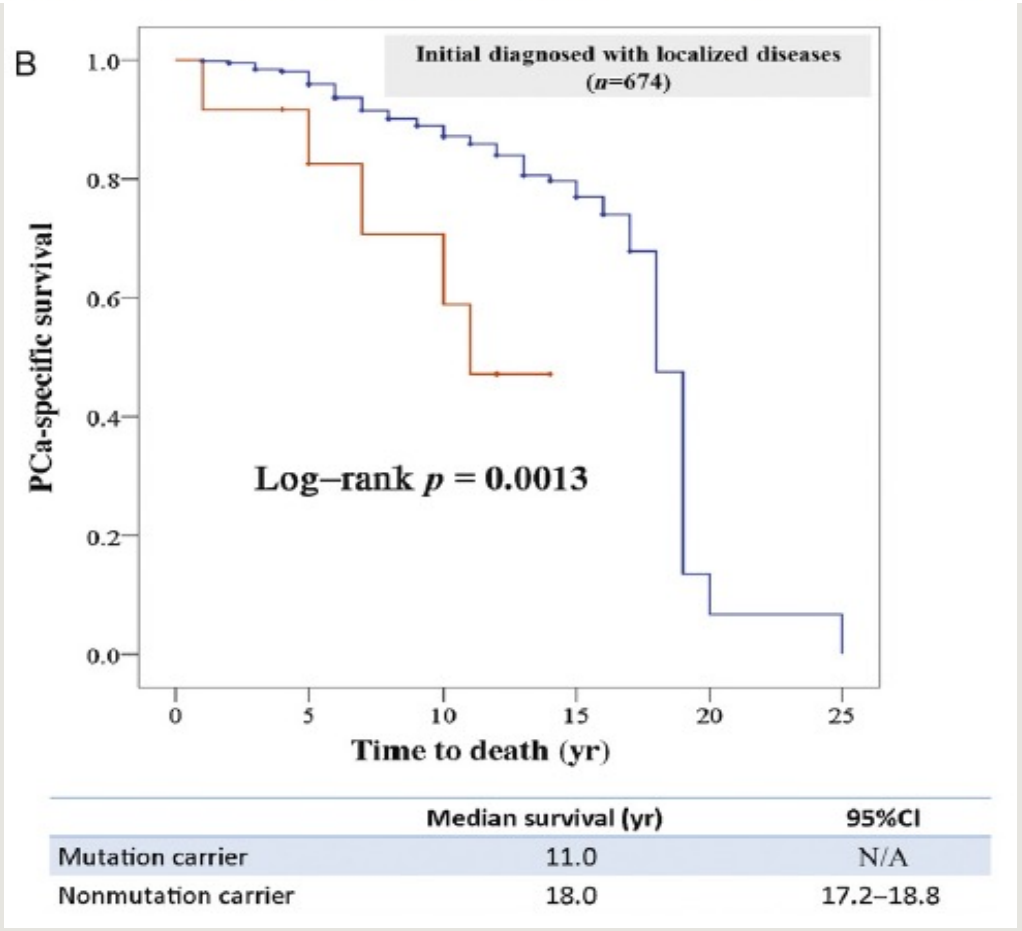
Giri JCO 2018, NCCN.org; American College of Medical Genetics and Genomics (ACMG)/National Society of Genetic Counselors (NSGC) practice guidelines.: https://www.acmg.net/docs/ACMG_Practice_Guideline_Referral_Indications_for_cancer_predisposition.pdf

BRCA 1/2 Mutations and CaP

- DNA damage response (DDR) genes
- 2-6 fold ↑ lifetime risk (BRCA2 > BRCA1)
- 8.6-fold ↑ risk by age 65 (BRCA2)
- PCa: Likely to be aggressive: Gleason 8 or higher, node +, mets, poor survival
- ↑ self and family risk for other hereditary cancers: breast, ovarian, melanoma, pancreatic, Lynch Syndrome, colon, gastric
- May direct mCRPC therapy (e.g, PARP inhibitors)

Germline Mutations in *ATM* and *BRCA1/2* Distinguish Risk for Lethal and Indolent Prostate Cancer and are Associated with Early Age at Death

Rong Na [a,b,†], S. Lilly Zheng [b,c,†], Misop Han [d,†], Hongjie Yu [b,e], Deke Jiang [b,e], Sameep Shah [b], Charles M. Ewing [d], Liti Zhang [d], Kristian Novakovic [b,c], Jacqueline Petkewicz [b,c], Kamalakar Gulukota [g], Donald L. Helseth Jr [g], Margo Quinn [b,c], Elizabeth Humphries [d], Kathleen E. Wiley [d], Sarah D. Isaacs [d], Yishuo Wu [a], Xu Liu [b,e], Ning Zhang [a,b], Chi-Hsiung Wang [b], Janardan Khandekar [g], Peter J. Hulick [f], Daniel H. Shevrin [f], Kathleen A. Cooney [h], Zhoujun Shen [i], Alan W. Partin [d], H. Ballentine Carter [d], Michael A. Carducci [i], Mario A. Eisenberger [i], Sam R. Denmeade [i], Michael McGuire [c], Patrick C. Walsh [d], Brian T. Helfand [b,c], Charles B. Brendler [b,c], Qiang Ding [a,], Jianfeng Xu [a,b,c,e,*], William B. Isaacs [d,i,*]*



	Median survival (yr)	95%CI
Mutation carrier	11.0	N/A
Nonmutation carrier	18.0	17.2–18.8

Eur Urol http://dx.doi.org/10.1016/j.eururo.2016.11.033

Therapeutic Options for Prostate Cancer

- Watchful waiting
- Surgery
- Radiation +/- Hormonal Ablation
  - External beam
  - 3D conformal
  - Brachytherapy

INITIAL RISK STRATIFICATION AND STAGING WORKUP FOR CLINICALLY LOCALIZED DISEASE[e]

Risk Group	Clinical/Pathologic Features See Staging (ST-1)			Additional Evaluation[h,i]	Initial Therapy
Very low[f]	Has all of the following: • cT1c • Grade Group 1 • PSA <10 ng/mL • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core[g] • PSA density <0.15 ng/mL/g			• Confirmatory testing can be used to assess the appropriateness of active surveillance (See PROS-F 2 of 5)	See PROS-3
Low[f]	Has all of the following but does not qualify for very low risk: • cT1–cT2a • Grade Group 1 • PSA <10 ng/mL			• Confirmatory testing can be used to assess the appropriateness of active surveillance (See PROS-F 2 of 5)	See PROS-4
Intermediate[f]	Has all of the following: • No high-risk group features • No very-high-risk group features • Has one or more intermediate risk factors (IRFs): ▸ cT2b–cT2c ▸ Grade Group 2 or 3 ▸ PSA 10–20 ng/mL	Favorable intermediate	Has all of the following: • 1 IRF • Grade Group 1 or 2 • <50% biopsy cores positive (eg, <6 of 12 cores)[g]	• Confirmatory testing can be used to assess the appropriateness of active surveillance (See PROS-F 2 of 5)	See PROS-5
		Unfavorable intermediate	Has one or more of the following: • 2 or 3 IRFs • Grade Group 3 • ≥ 50% biopsy cores positive (eg, ≥ 6 of 12 cores)[g]	Bone and soft tissue imaging[j,k] • If regional or distant metastases are found, see PROS-8 or PROS-12	See PROS-6
High	Has no very-high-risk features and has exactly one high-risk feature: • cT3a OR • Grade Group 4 or Grade Group 5 OR • PSA >20 ng/mL			Bone and soft tissue imaging[j,k] • If regional or distant metastases are found, see PROS-8 or PROS-12	See PROS-7
Very high	Has at least one of the following: • cT3b–cT4 • Primary Gleason pattern 5 • 2 or 3 high-risk features • >4 cores with Grade Group 4 or 5			Bone and soft tissue imaging[j,k] • If regional or distant metastases are found, see PROS-8 or PROS-12	See PROS-7

All guidelines now give recommendations for AS for suitable candidates with favorable intermediate risk

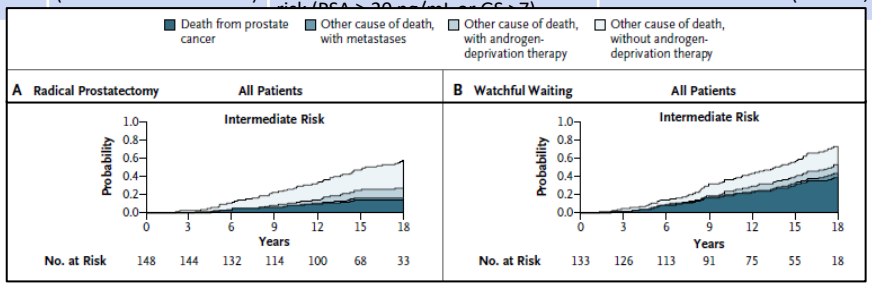
Carlsson S, Eastham J. *BMC Urol* 2021 (submitted)

In SPCG-4 and PIVOT, radical prostatectomy conferred a benefit over Watchful Waiting for men with intermediate risk

Of note:

- The trials also included men with unfavorable features
- The WW strategy was different from AS with no option of curative treatment

RCT	Ref	Years	Sample size	Patient selection	Oncologic outcomes
SPCG-4	Bill-Axelson et al (2014)	1989-1999	RP: N=347 (148 intermediate risk) WW: N=348 (133 intermediate risk)	Low/Intermediate/High risk Intermediate risk: not meeting criteria for low risk (PSA < 10 ng/mL & GS <7 or WHO grade 1) or high risk (PSA > 20 ng/mL or GS > 7)	At 18 years (RP vs. WW): For intermediate risk: Prostate cancer mortality: **24.2% reduction** 95% CI 13.6 to 34.9% (**RR 0.38**, p<0.001)



In ProtecT, there were few PCa deaths at 10 years and no differences by treatment arm (RP, RT or PSA-based monitoring) or disease risk at diagnosis

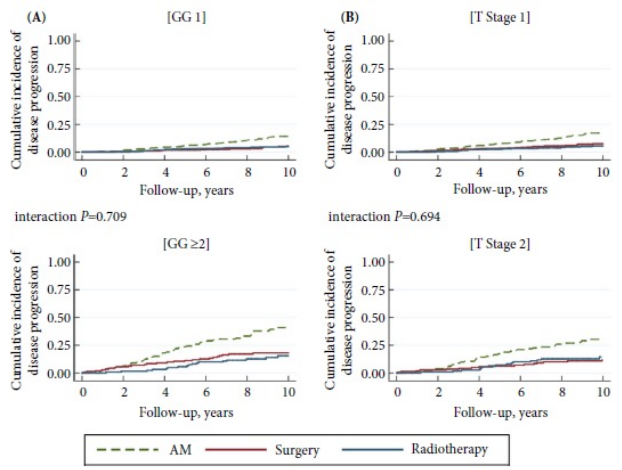
RCT	Ref	Years	Sample size	Patient selection	Oncologic outcomes
ProtecT	Hamdy et al (2016), Bryant et al (2020)	1999-2009	RP: N=553 (120 GS 7) RT: N=545 103 (GS 7) Active Monitoring: N=545 (111 GS 7)	Low/Intermediate/High risk Intermediate risk: GS 7 (Grade Group 2–3), a PSA level > 10 & ≤ 20 ng/mL, or T2b disease.	At 10 years (RP vs. Active Monitoring): The number of deaths were few and there were **no significant differences** in the number of deaths from prostate cancer by treatment arm

Deaths from prostate cancer at 10 years:
RP n=5
RT n=4
AS n= 8

- 5 Gleason 7, 3 Gleason 6
- 5 T1c, 3 T2
- All PSA <10 ng/mL

Risks of progression and metastases were increased in the AS arm

Longer follow-up is awaited

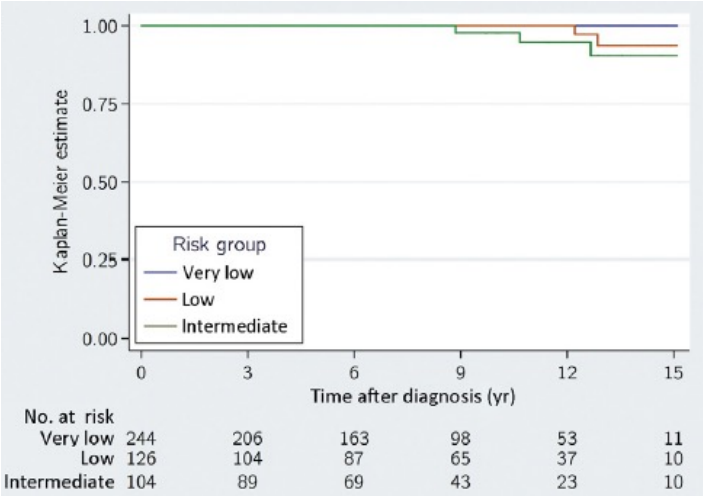


Göteborg cohort

15-year PCa-specific survival:

- **Intermediate risk: 90% (95% CI 72%-97%) (4 deaths)**
- **Low risk: 94% (95% CI 77%-98%) (2 deaths)**

- 474 men diagnosed with screen-detected prostate cancer in the Göteborg-1 trial between 1995-2014 managed with AS
- 104 men with intermediate risk PCa
- Median follow-up 8 years



Godtman RA, *Eur Urol* 2016

External Beam Radiation Therapy: Role of Androgen Deprivation

Optimal duration

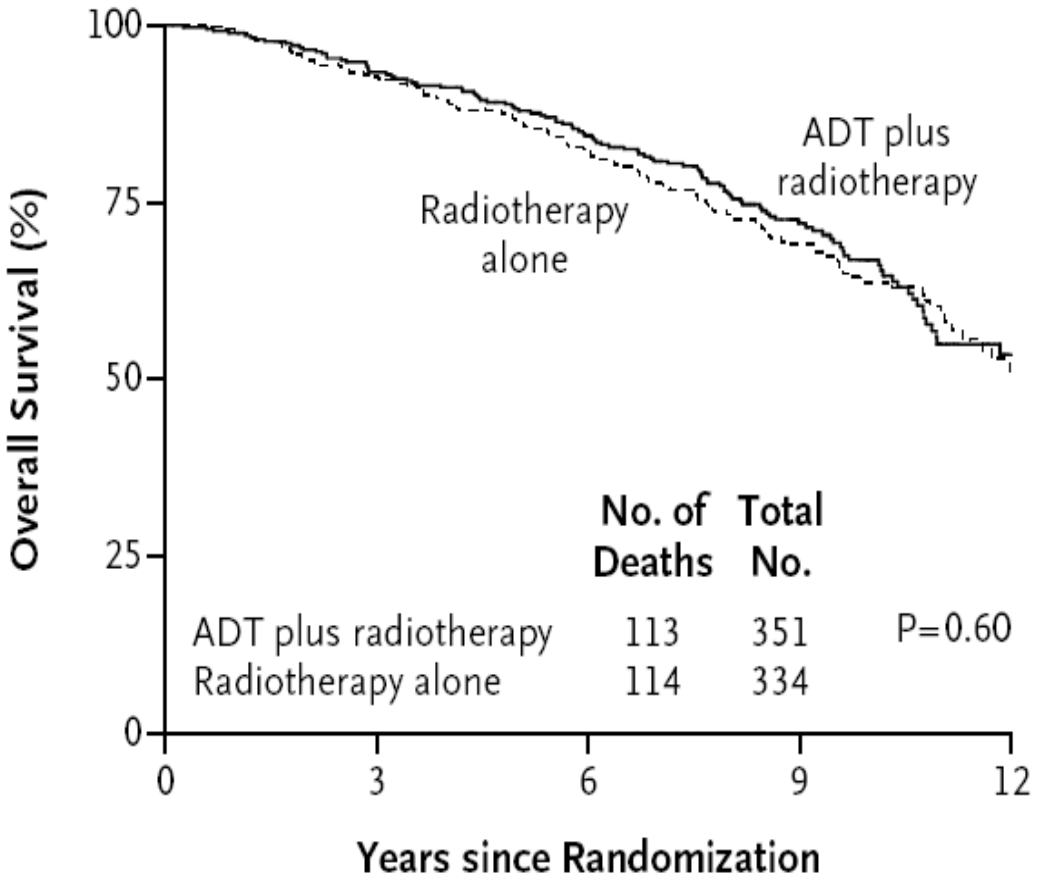
- *When the local control with radiation alone is good:*
  never

- *When the risk of local failure is high:*
  3-6 months as a radiation sensitizer

- *When the risk of distant disease is high:*
  2-3 years of treatment

ADT *Does Not* Improve Survival in Men Receiving Radiation for Low-Risk Disease

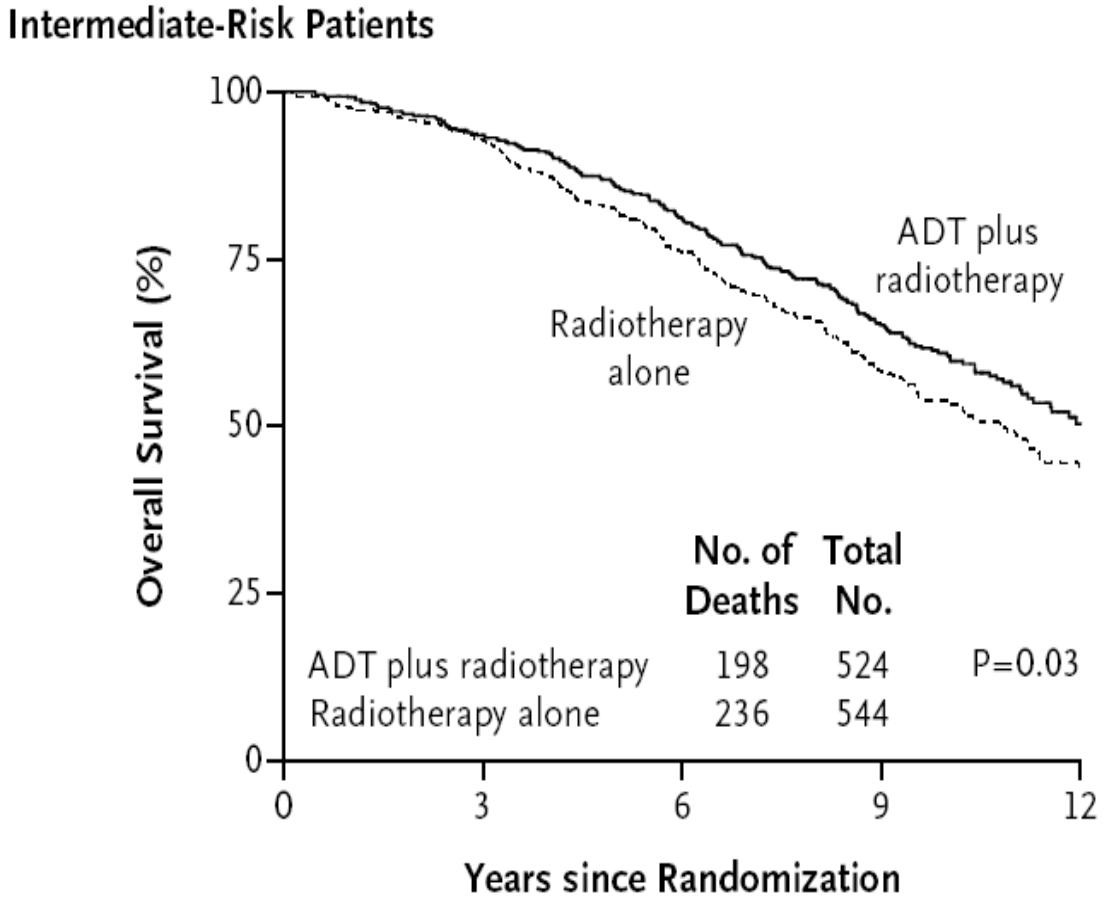
RTOG 94-08
Low Risk



Jones et al (2011) N Engl J Med 365:107-118

Short-Term ADT Improves Survival in Men Receiving Radiation for Intermediate-Risk Disease

RTOG 94-08 Intermediate Risk



Jones et al (2011) N Engl J Med 365:107-118

Current Summary Recommendations Definitive Setting

Risk group	Definition	Radiotherapy recommendation	ADT recommendation
Low risk	NCCN	Surveillance/brachytherapy/EBRT	None
Low-intermediate risk†	Gleason 3+4; <50%+ cores; PSA <10	Surveillance/brachytherapy/EBRT	None
High-intermediate risk†	Gleason 4+3; >50%+ cores; PSA 10–20	EBRT ± brachytherapy	4-6 months GnRH agonist
High risk	NCCN	EBRT ± brachytherapy	24 months GnRH agonist†

†, based on emerging data; further clinical data forthcoming. In all cases, ADT to start ~8 weeks prior to radiation. ADT, androgen deprivation therapy; NCCN, National Comprehensive Cancer Network; GnRH, gonadotropin releasing hormone; PSA, prostate-specific antigen; EBRT, external beam radiation therapy.Krause et al. Transl Androl Urol. 2018 Jun; 7(3): 378–389

Conclusions

- Prostate cancer is the most commonly diagnosed cancer in men in the United States in 2024, and the second leading case of cancer death.
- A decision to screen a patient should weight the risks and benefits of local therapy
- Active surveillance can be considered in patients with low-risk prostate cancer.
- Local treatment decisions should be based on the patients the side effect profile of the respective treatment
- Androgen deprivation therapy should be administered along with radiation therapy for intermediate/high risk localized prostate cancer patients.
- Genetic counselling should be offered to men with localized prostate cancer