



SCHOOL OF MEDICINE  
VANDERBILT UNIVERSITY

# Comparative Effectiveness Research in Localized Prostate Cancer: Finding the Middle Way

David F. Penson, MD, MPH  
Professor of Urologic Surgery  
Director, Center for Surgical Quality and Outcomes Research  
Vanderbilt University Medical Center  
Nashville, TN

# CER in Localized PCa: Shortcomings of RCTs

- Accrual difficulties
  - PIVOT and SPIRIT experience
- Generalizeability concerns
  - ProtecT invited 225,000 men to participate in screening study as a lead-in to ProtecT trial, roughly 50% participated
  - Roughly 65% of those eligible for inclusion for ProtecT participated
  - Applicability of SPCG4 (and possibly PIVOT) results to men diagnosed in US in 2010 is unclear

# CER in Localized PCa: Shortcomings of RCTs

- Unable to account changing approaches
  - Robotic prostatectomy not studied in RCTs
  - Radiotherapy arms do not include IMRT, proton beam therapy or brachytherapy
  - Watchful waiting is NOT active Surveillance
- Unable to control for quality of intervention
  - Outcomes of surgery and radiation are influenced by center/surgeon volume
  - Processes of care that can influence results not included in or controlled for RCT protocols

# Surgeon Volume And Outcomes Following Radical Prostatectomy

Table 2. Relationship of Surgeon Volume to Outcomes after Surgery for Prostate Cancer\*

Outcome	Odds Ratio of Outcome per Decline in Individual Surgeon Volume in 100-Unit Volume Intervals (95% CI)			
	Adjusted for Case Mix	Adjusted for Case Mix and Hospital Volume	Corrected for Clustering of Outcomes within Individual Surgeon†	
			GEE Method‡	Random-Effects Method§
Postoperative complications	1.73 (1.40–2.15)	1.58 (1.25–2.00)	1.58 (1.16–2.17)	1.45 (1.00–2.14)
<i>P</i> value	<0.001	<0.001	0.004	0.049
Late urinary complications	2.77 (2.19–3.51)	2.32 (1.80–2.99)	2.32 (1.34–4.01)	1.88 (1.19–2.97)
<i>P</i> value	<0.001	<0.001	0.002	0.007

\* GEE – generalized estimating equation.

† Corrected for clustering after adjustment for case mix and hospital volume.

‡ Calculated by using the GENMOD procedure in SAS (SAS Institute, Inc., Cary, North Carolina).

§ Calculated by using the gllamm6 command in Stata (Stata Corp., College Station, Texas).

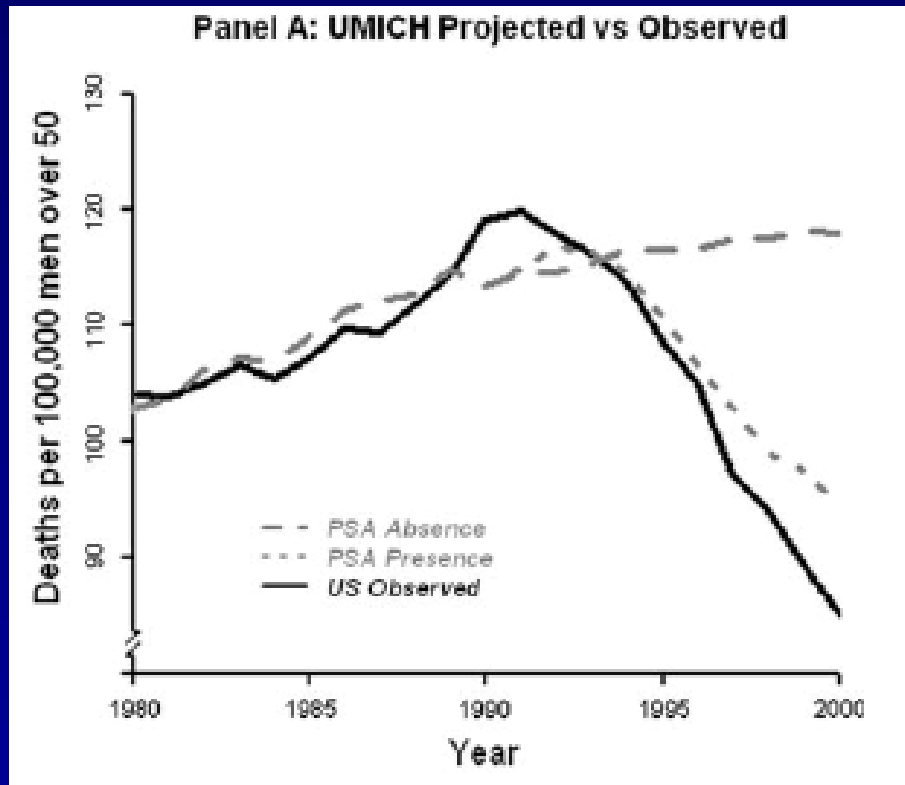
# CER in Localized PCa: Shortcomings of Simulation Modeling

- Clinicians and patients tend to be skeptical/wary of results
  - Methods are often are not transparent
  - “Lies, damn lies and statistics”
- Different assumptions and model characteristics can lead to differing results
  - How can confident can we be in our estimates of health state utility assessments?
  - Sensitivity analysis only addresses this somewhat
  - What is the “truth/reality”?

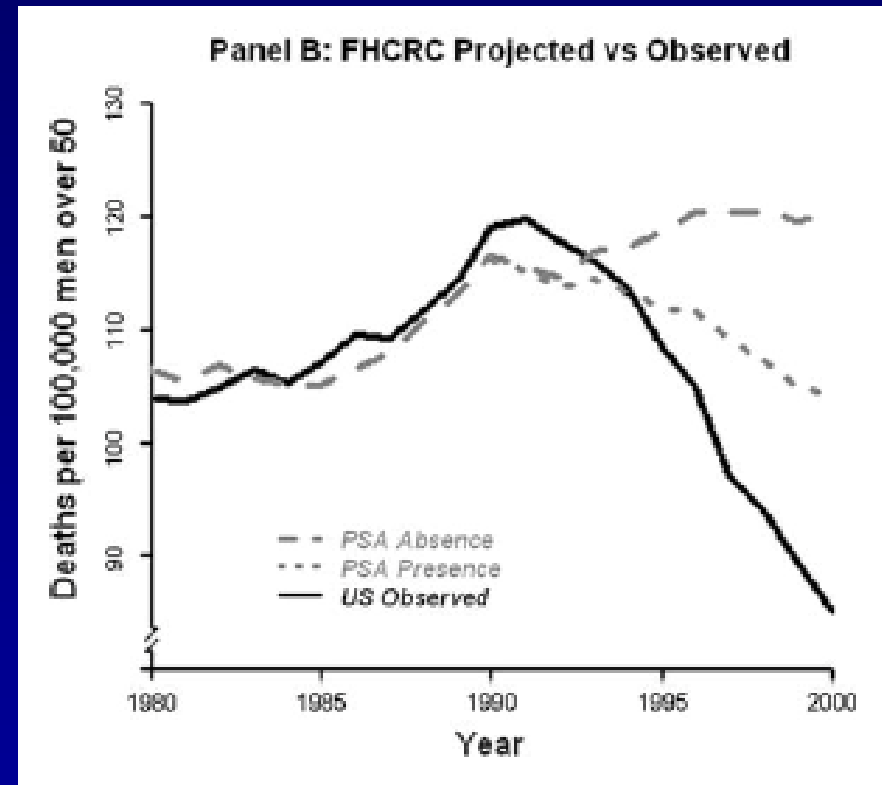
# Quantifying the role of PSA screening on CaP mortality decline

- Two previously developed computer simulation models were used
  - FHCRC
  - UMich
- Models painstakingly calibrated with existing data to estimate natural history of disease and growth of PSA
- 1980-2000 SEER incidence and NCHS mortality data used to populate models

# Quantifying The Role Of PSA Screening On Cap Mortality Decline



70% of mortality decline due to screening

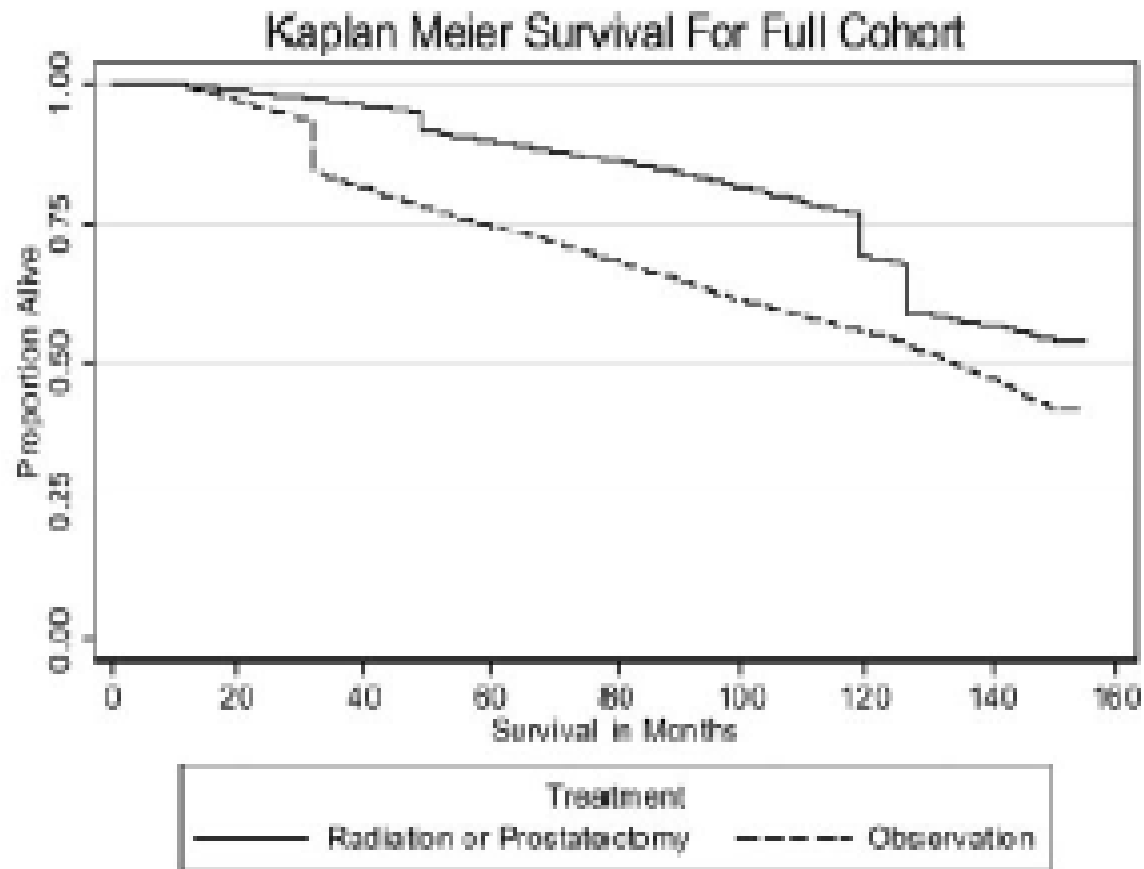


45% of mortality decline due to screening

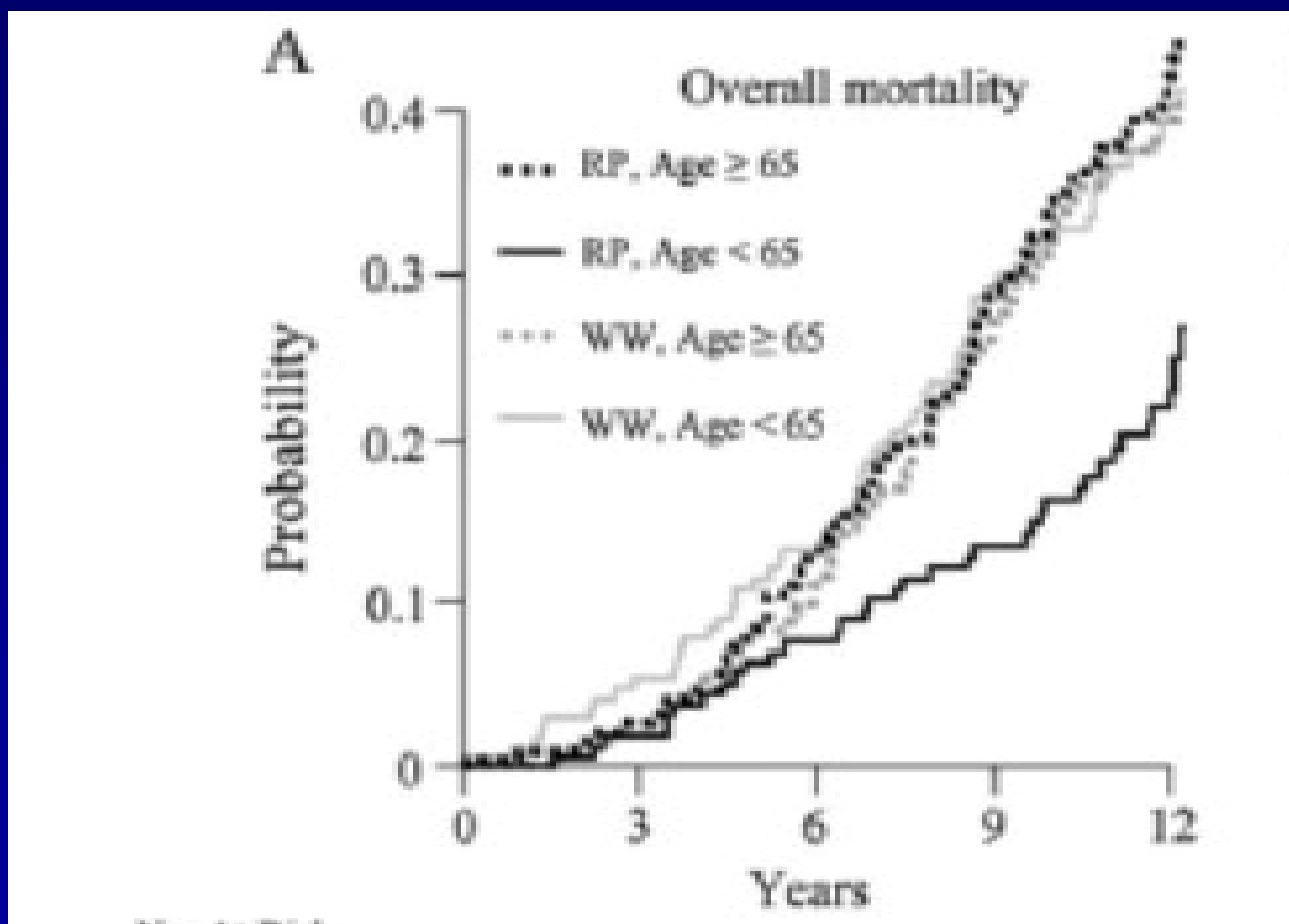
# CER in Localized PCa: Shortcomings of Observational Studies

- Like RCTs, results can be dated
  - PCOS often criticized for having older XRT doses and techniques
- Outcomes not always optimal
  - Hu, et al studies of open vs. robotic RP using impotence and incontinence codes in SEER-Medicare
- Selection bias
  - Risk-adjustment VERY challenging

# Active therapy vs Observation. Observational Study Using SEER- Medicare



# Surgery vs Observation: Results from SPCG 4 study



# CER in Localized PCa: Finding the Middle Way

- All three study designs are informative and necessary
- RCTs and models are needed and beneficial but...
- IMPROVED observational studies are critical to inform decision-making
  - Allows for assessing new technologies
  - Facilitates subgroup analyses
  - Helps in tailoring the data to the individual patient

# The CEASAR study:

## Comparative Effectiveness Analysis of Surgery And Radiation in localized prostate cancer

- “Hybrid” observational study design
  - 4 tumor registries (LA, Louisiana, NJ, ATL) using a population-based approach
  - CaPSURE observational disease registry using a convenience sample approach focused on novel technologies (IGRT, HIFU, etc)
- Approximately 4200 subjects with localized disease will be accrued over 12-18 months

# The CEASAR study:

## Comparative Effectiveness Analysis of Surgery And Radiation in localized prostate cancer

- Designed to study “what works, in which patients and in whose hands”
- Outcomes include HRQOL, other PROs, complications and cancer control
- Focus is on aggressive interventions, as opposed to active surveillance (although AS subjects will obviously be included)

# Unique Strengths of The CEASAR study

- Data collection from numerous sources
  - Patient-reported data, medical records and SEER
  - Detailed information on surgical and radiation intervention
- Focus on the quality of the intervention
  - Data will be collected on structure and process measures to control for quality in analysis
- Non-traditional patient reported measures will be tested for risk adjustment
  - Social support, decision-making, PC anxiety
- Use of hybrid design allows study of new techniques will maintaining comparability to other cohorts (i.e., PCOS)

# CER in Localized PCa: WALKING THE MIDDLE WAY

- All three study designs are necessary in CER in localized PCa
- Overvaluing one over the other two will lead to biased conclusions
- The real challenge lies not only in developing the evidence, but in reconciling studies and assimilating the data in such a way that patients can use the information to make personalized decisions in this heterogeneous disease.