

Systematic Review: Comparative Effectiveness & Harms of Treatments for Clinically Localized Prostate Cancer

Timothy J. Wilt, MD, MPH

Minnesota-AHRQ

Evidence based Practice Center



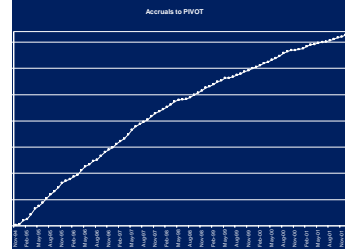
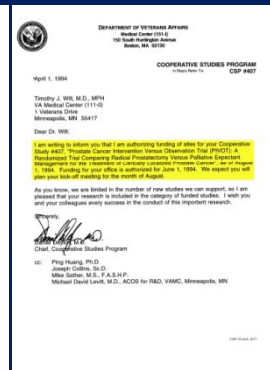
Context

- Prostate cancer is common and a potentially serious health condition
- Incidence increased, patient & disease characteristics changed and treatment options multiplied since PSA testing began
- Sorting through the benefits and harms of treatment strategies for clinically localized prostate cancer is difficult

Goals

- Describe CER of treatments for localized CaP
- Highlight evidence limitations/gaps:
 - Study design
 - *Population, Intervention, Comparator, Outcome, Timing, Setting*
- Discuss ongoing RCTs (& challenges) that may inform clinical, research and health policy decision making
- Summarize future research needed to close evidence gaps

1947
Millin first described RRP



1982

Walsh developed nerve sparing technique

1993

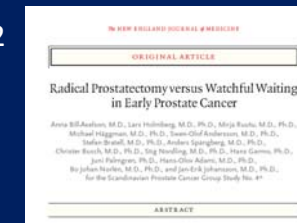
Blessings from Drs. Madsen & Whitmore

April, 1994

PIVOT study approved for funding

January, 2002

Recruitment Ends
731 enrolled



September, 2005
SPCG-4 8-yr results



1904
Young first RP for CaP



1966
Huggins wins Nobel prize for hormonal basis of CaP

1960's- 70s

VACURG studies Re: CaP Tx begin



1990's

1988
VACURG studies report RP vs. WW



December, 1992
PIVOT planning approved

November, 1994
PIVOT begins, Tampa VA enrolls 1st patient

September, 2001
SPCG-4 publishes 5-yr results



Large Number of Additional Men Diagnosed and Treated Since Start of PSA screening

Age group, y	No. of additional men diagnosed	No. of additional men treated		
		Surgery	Radiation	Either or both
20–49	50 500	33 800	10 700	42 200
50–59	325 100	194 400	90 800	273 000
60–69	610 100	273 900	221 300	475 200
70–79	386 600	69 700	167 100	227 500
>80	–66 700	–700	–12 500	–13 200
Total	1 305 600	571 000	477 400	1 004 800

Welch JNCI, 2009

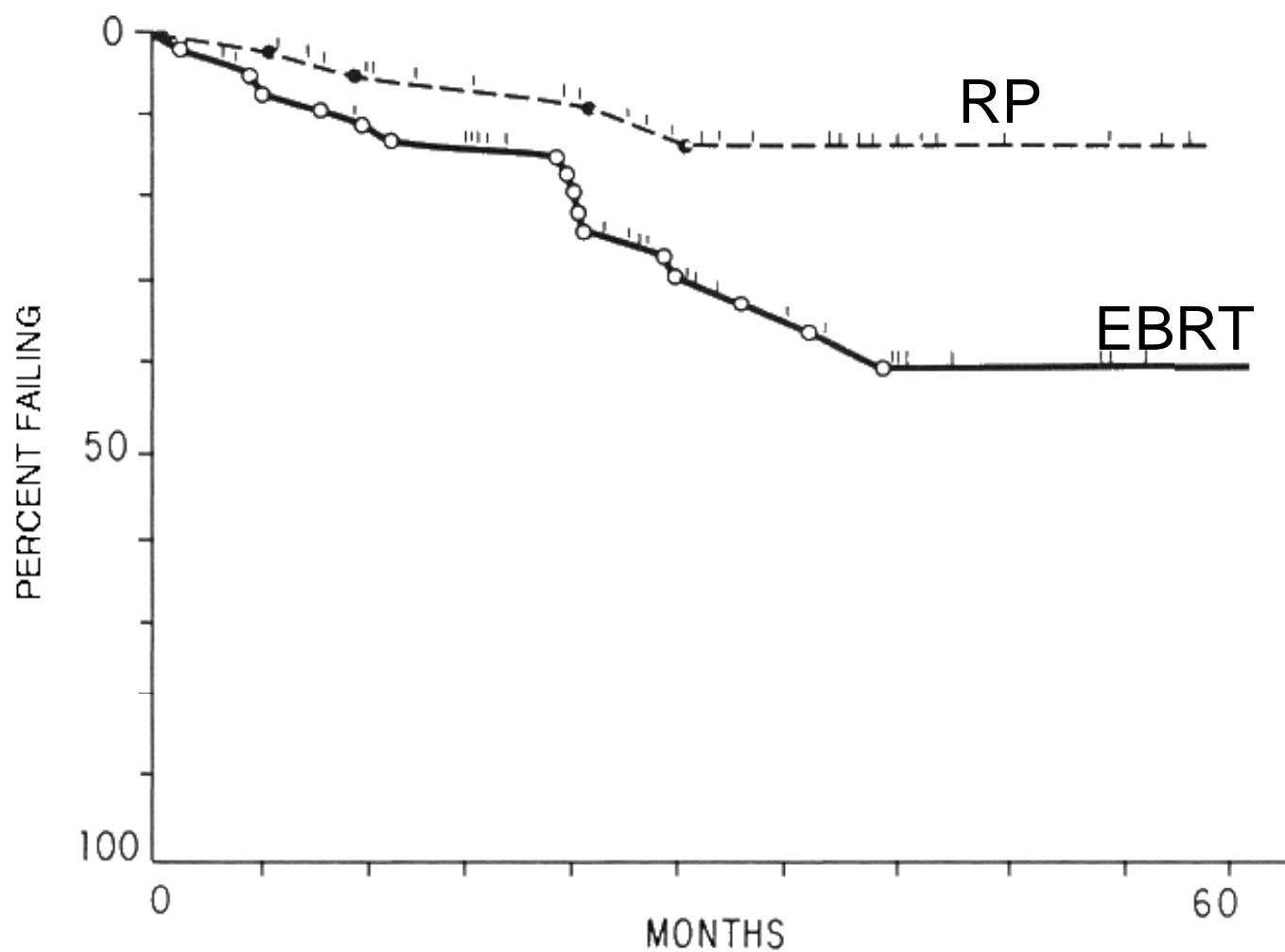
AHRQ-EPC CER Methods

- Develop analytic framework
- Identify & refine key questions
 - Utilize Key Informants & TEP
- Create CER research protocol
 - Inclusion criteria
 - English language
 - Clinically localized CaP (T1-T2)
 - RCTs through 2007
 - Nonrandomized reports thru 2004
 - Additional harms using population based reports through 2007
 - Emerging technologies through 2007

Methodological problems

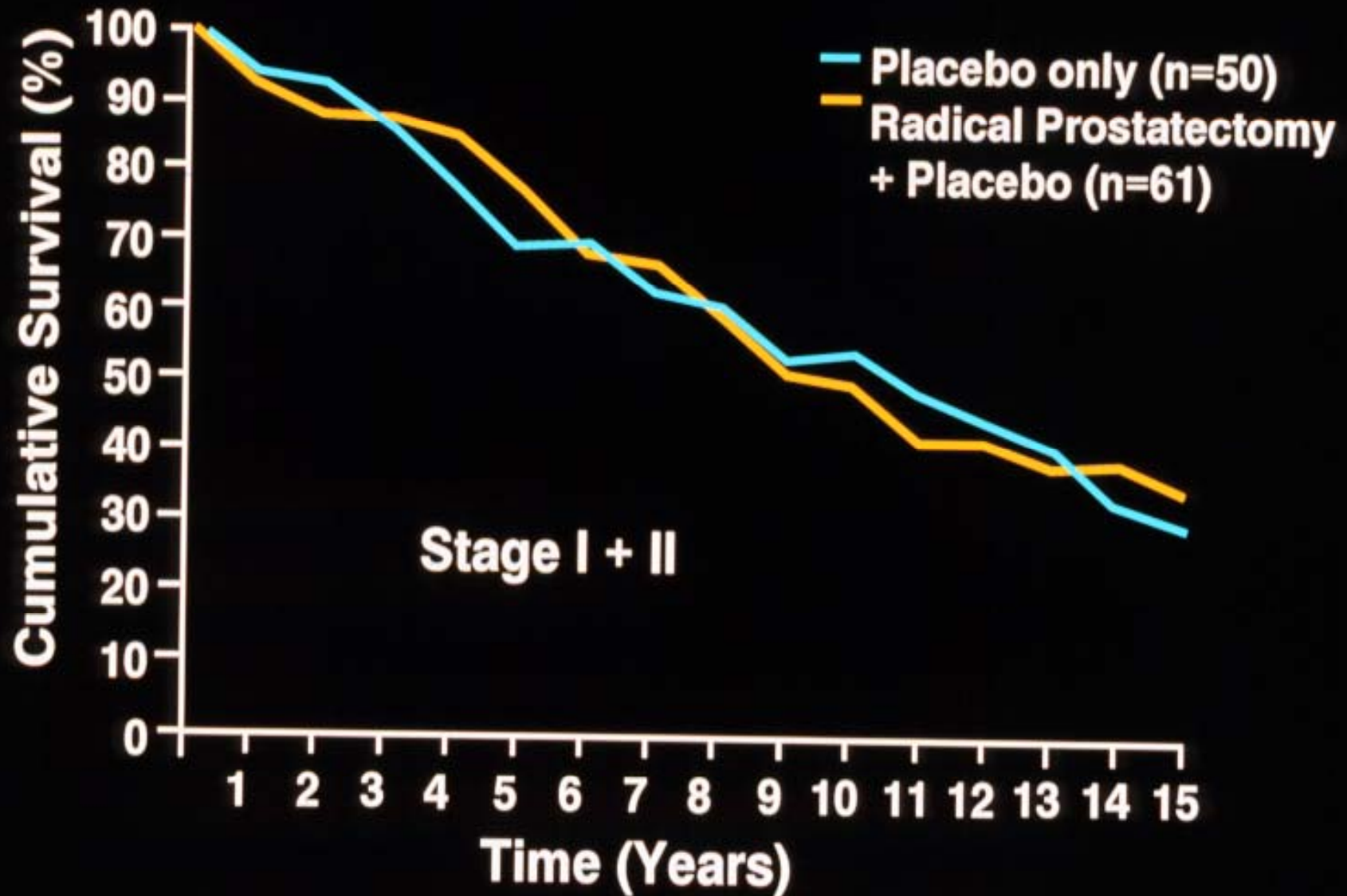
- Large volume → Low quality
 - 14,000 relevant articles → 18 RCTs; 473 observational
- RCTs
 - Few in number
 - Rarely compared one major treatment vs. another
 - Sample size & follow-up length inadequate
 - Some in pre-PSA era
 - None for “emerging technologies”
- NonRCTs:
 - Multiplicity & selectivity of study reporting
 - Varied greatly in:
 - Effectiveness & harms estimates
 - Frequency & definitions of reported outcomes
 - Lacked controls , risk adjustment & pt/tumor characteristics

Radical Prostatectomy versus Radiation Time to Treatment Failure (n = 97)



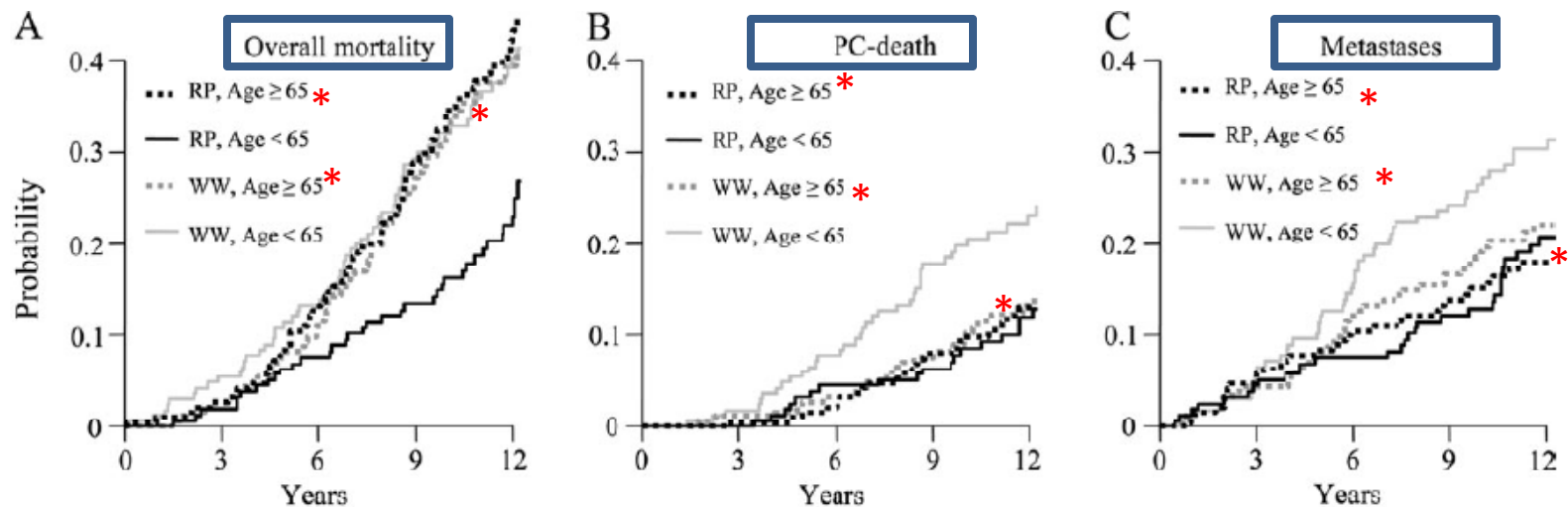
Paulson, et al. J. Urol, 1982

Prostatectomy Versus Expectant Management VACURG-RCT

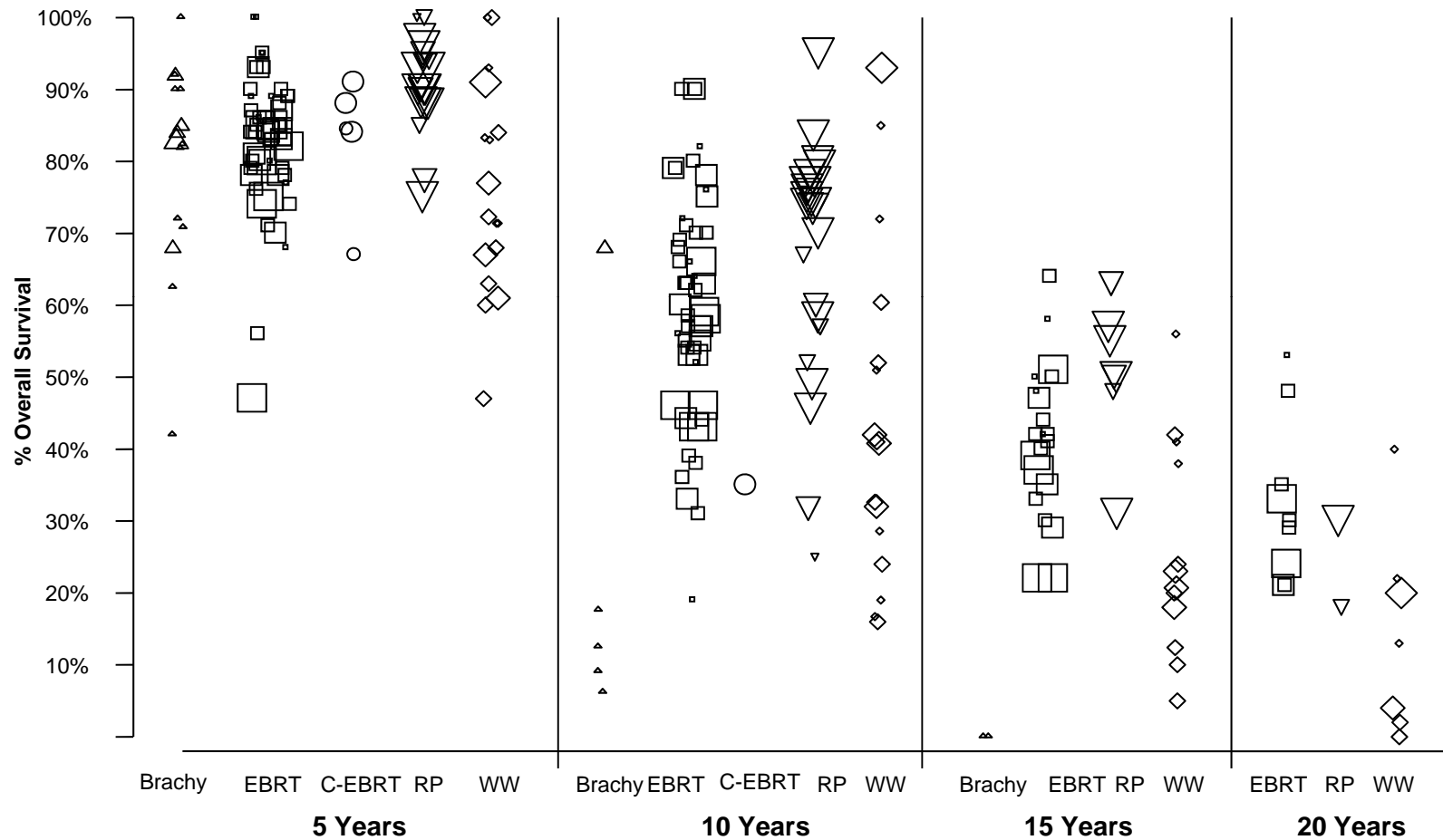


Radical Prostatectomy Versus Watchful Waiting in Localized Prostate Cancer: the Scandinavian Prostate Cancer Group-4 Randomized Trial

Anna Bill-Axelsson, Lars Holmberg, Frej Filén, Mirja Ruutu, Hans Garmo, Christer Busch, Stig Nordling, Michael Häggman, Swen-Olof Andersson, Stefan Bratell, Anders Spångberg, Juni Palmgren, Hans-Olov Adami, Jan-Erik Johansson; for the Scandinavian Prostate Cancer Group Study Number 4

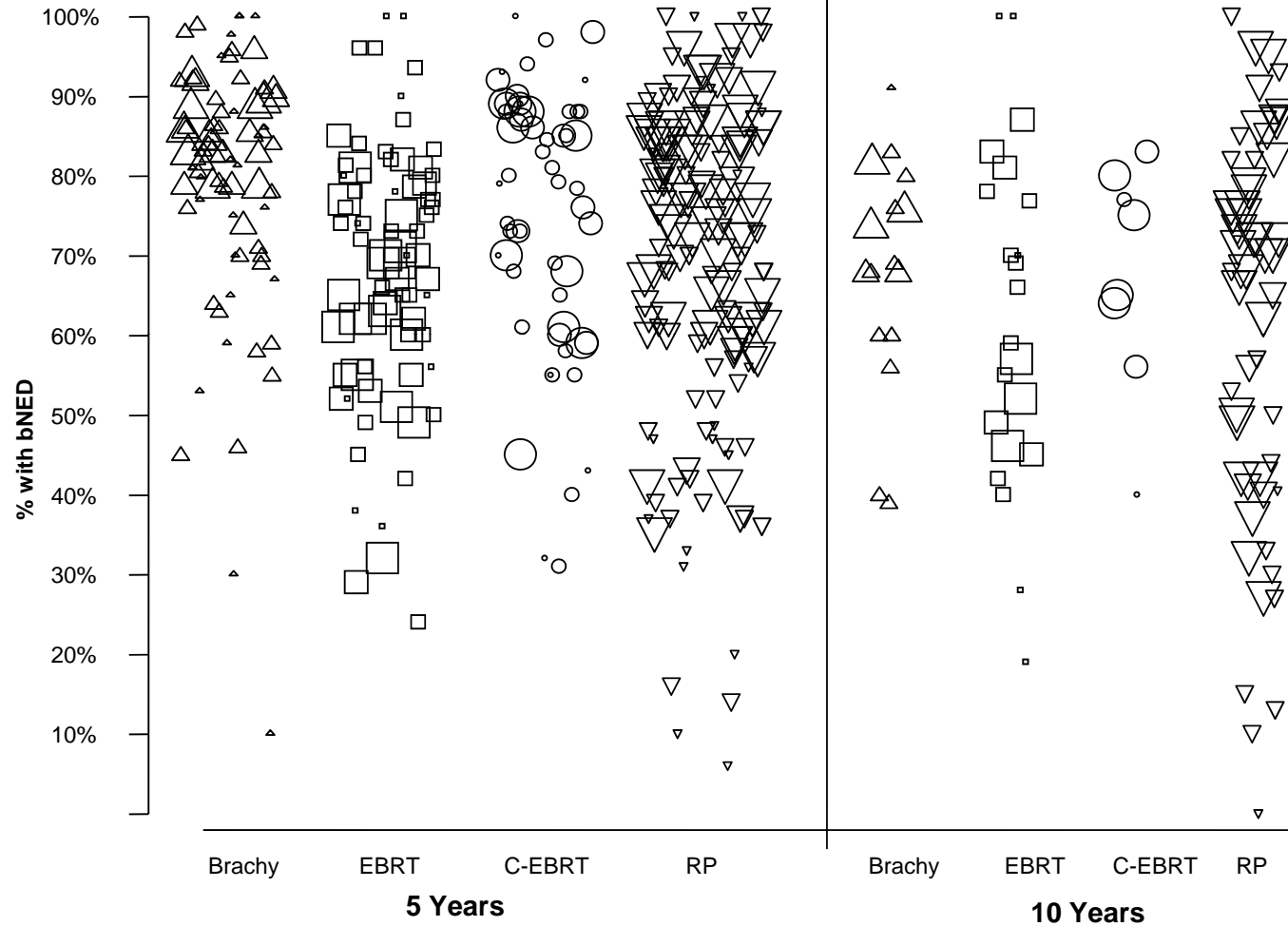


Overall survival by treatment (5, 10, 15, 20 years)



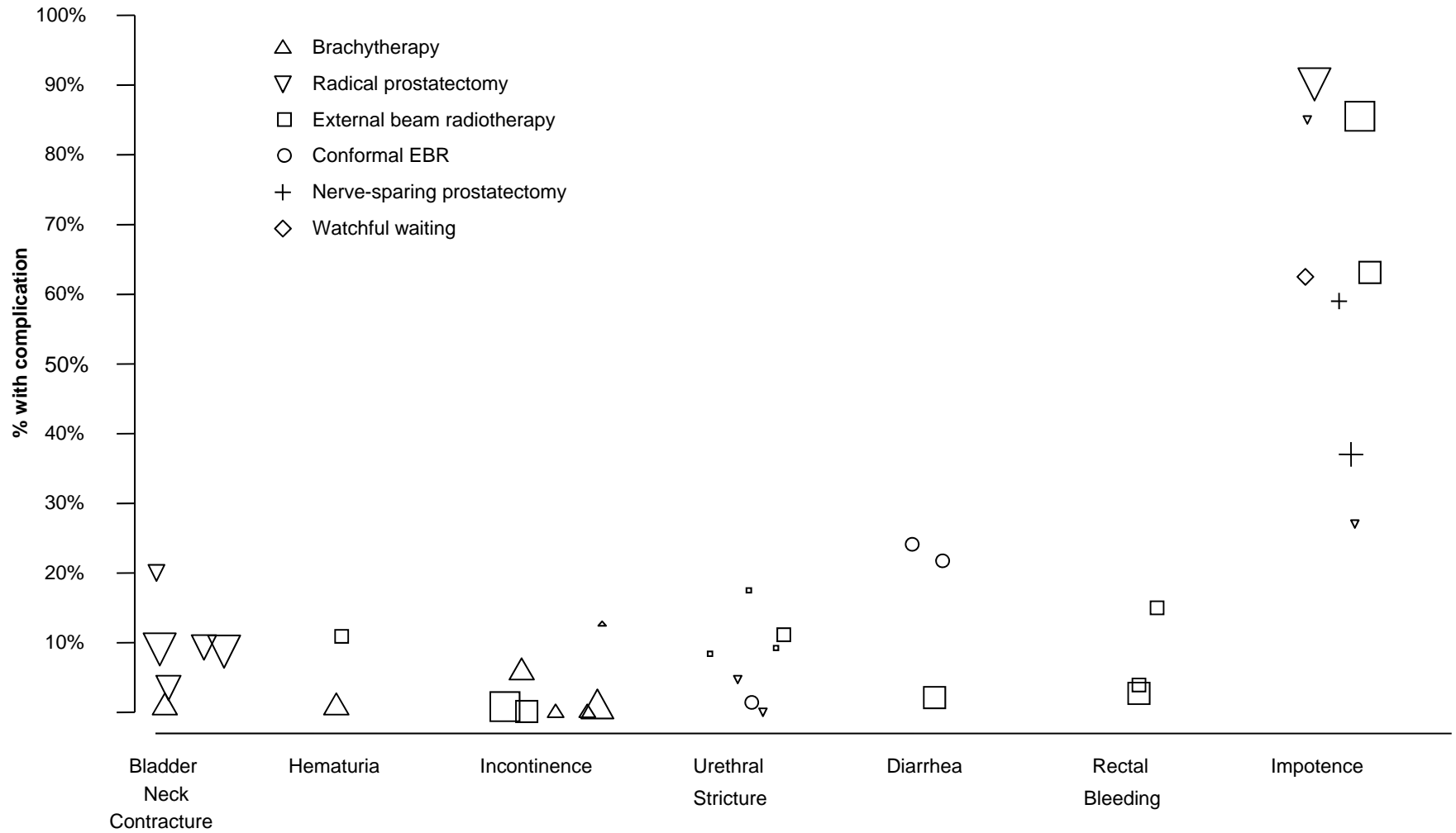
Brachy = Brachytherapy; EBRT = External Beam Radiotherapy; C-EBRT = Conformal External Beam Radiotherapy, RP = Radical Prostatectomy; WW = Watchful Waiting

Biochemical no evidence of disease at 5 & 10y by treatment (all definitions)



Brachy = Brachytherapy; EBRT = External Beam Radiotherapy; C-EBRT = Conformal External Beam Radiotherapy; RP = Radical Prostatectomy
 Point size indicates N, <50 (smallest), 50-150 (next smallest) 150-300 (next largest) and >300 (largest)

Complications by treatment



Point size indicates N, <50 (smallest), 50-150 (next smallest) 150-300 (next largest) and >300 (largest)

AHRQ-EPC

Future Research Needs Project

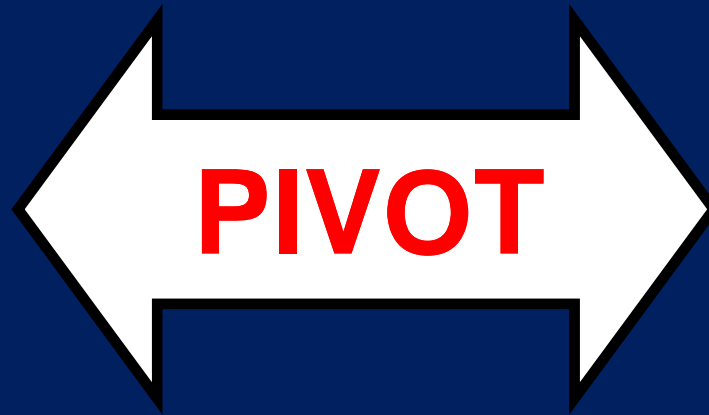
- Identify which patients to treat
- Comparative Effectiveness of Treatments
- Factors Impacting Treatment Decisions
- Methodologic Challenges

Rothenberg BM, et al. BCBCSA TEC EPC 2010

www.effectivehealthcare.ahrq.gov/reports/final.cfm



**VA, NCI, AHRQ Cooperative Study #407:
Prostate cancer
Intervention Versus Observation Trial
(PIVOT)**



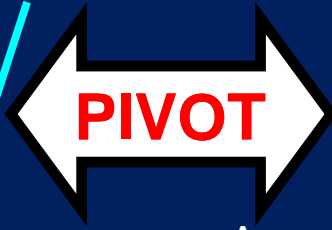
**Randomized trial of radical prostatectomy versus
expectant management for the treatment of
clinically localized prostate cancer**

Endpoints

- **Primary endpoint**
 - All-cause mortality
- **Secondary endpoints**
 - CaP & Tx Mortality
 - Metastatic progression
 - CaP & Tx Morbidity
 - Local & Regional progression
 - Treatments utilized
 - Bladder, bowel, sexual dysfunction
 - Quality of life (overall & DZ specific)

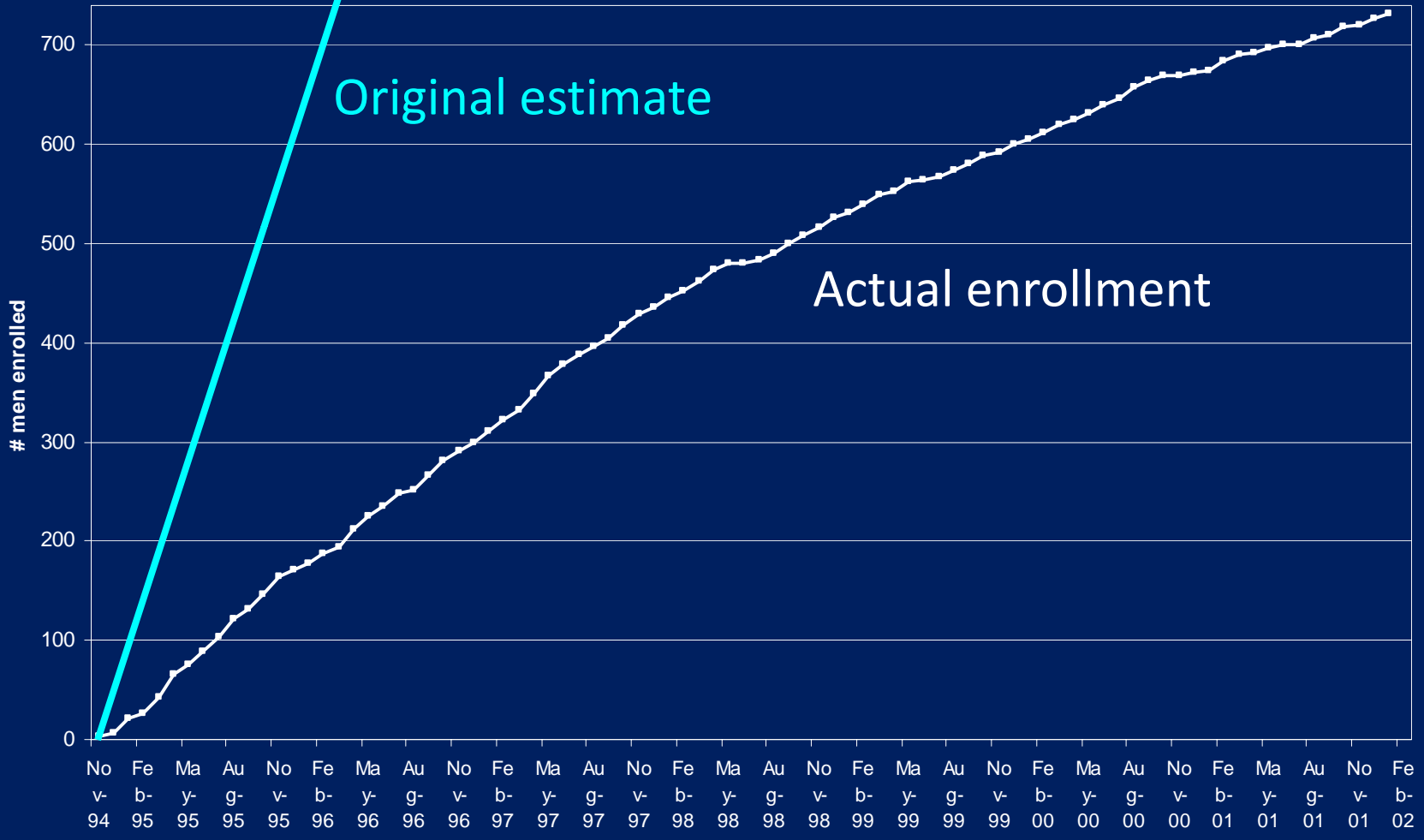
“I am afraid that although this is an excellent question...I would recommend that this proposal not be entertained, because in my opinion it would never be completed”

Anonymous CSP Reviewer, 1992



Recruitment

Accruals to PIVOT



PIVOT enrollees vs. men eligible but decline randomization

<u>Characteristic</u>	<u>PIVOT (n=731)</u>
• Age (years)	67
• Race	
White	62
Black*	32
Hispanic	4
• PSA (ng/mL)	
Mean	10.1
Median	7.8
• Histologic grade	
Well*	25
Moderate	62
Poor	7
• Health Status	
Excellent-VG	56
Good	32
Fair	12

Conclusions

- Determining Comparative Effectiveness and Harms of localized prostate cancer treatments is difficult due to limitations in the evidence
- Prostate cancer & their treatments represent unique challenges though lessons apply to other diseases & treatments
- Observational data, surveys, modeling & biorepositories using standardized protocols beneficial but...
- Completion of ongoing RCTs is necessary
 - PIVOT
 - ProtecT
 - START