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*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Odds Ratio of Outcome per Decline in Individual Surgeon Volume in 100-Unit Volume Intervals (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted for Case Mix</td>
</tr>
<tr>
<td>Postoperative complications</td>
<td>1.73 (1.40–2.15)</td>
</tr>
<tr>
<td></td>
<td>P value</td>
</tr>
<tr>
<td>Late urinary complications</td>
<td>2.77 (2.19–3.51)</td>
</tr>
<tr>
<td></td>
<td>P value</td>
</tr>
</tbody>
</table>

*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 glamm6 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 not transparent
  – “Lies, damn lies and statistics”

• Different assumptions and model characteristics can lead to differing results
  – How can we be confident 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

Etzioni, et al, Cancer Causes Control, 2008
Quantifying The Role Of PSA Screening On Cap Mortality Decline

70% of mortality decline due to screening

45% of mortality decline due to screening

Etzioni, et al, Cancer Causes Control, 2008
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

Wong, et al, JAMA 2006
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.