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Systematic Review of Active Surveillance & Radical Prostatectomy for Low-Risk Prostate Cancer: Preliminary Findings

May 5, 2009

Dan Ollendorf, MPH, ARM
Chief Review Officer

Systematic Review Objectives

- To compare potential clinical benefits, harms of active surveillance (AS) and radical prostatectomy (RP) among low-risk prostate cancer patients
- To examine benefits, harms by surgical approach
- To examine rate of disease-related symptom progression on AS
- To review evidence in context with prior appraisal of radiation alternatives

Review Scope

- Patients with low-risk disease (D'Amico criteria):
  - Stage T1-T2a
  - Gleason score ≤6
  - PSA <10 ng/mL
- Treatments of interest:
  - Active surveillance
    - Distinguished from watchful waiting by decision to treat upon evidence of local progression
  - Radical prostatectomy
    - Open (RRP)
    - Laparoscopic (LRP)
    - Robot-assisted laparoscopic (RALP)

Major Exclusions

- Study types:
  - Without identifiable low-risk subgroup or preponderance of low-risk participants
  - Sample size <50, or outcomes reported in <50 patients
  - Open perineal prostatectomy
  - Non-English language
  - Publications prior to 1996 (to capture current spectrum of incident cases)

Outcomes Assessed

- Survival:
  - Overall
  - Disease-specific
  - “Treatment-free” (AS only)
- Freedom from biochemical recurrence (RP only)
  - Typically calculated based on presence of PSA level greater than nadir (e.g., 0.2)

Outcomes Assessed

- Health-related QoL
- Symptoms/Harms (AS):
  - Progression of obstructive urinary symptoms
  - Progression of erectile dysfunction
  - Effects of patient anxiety

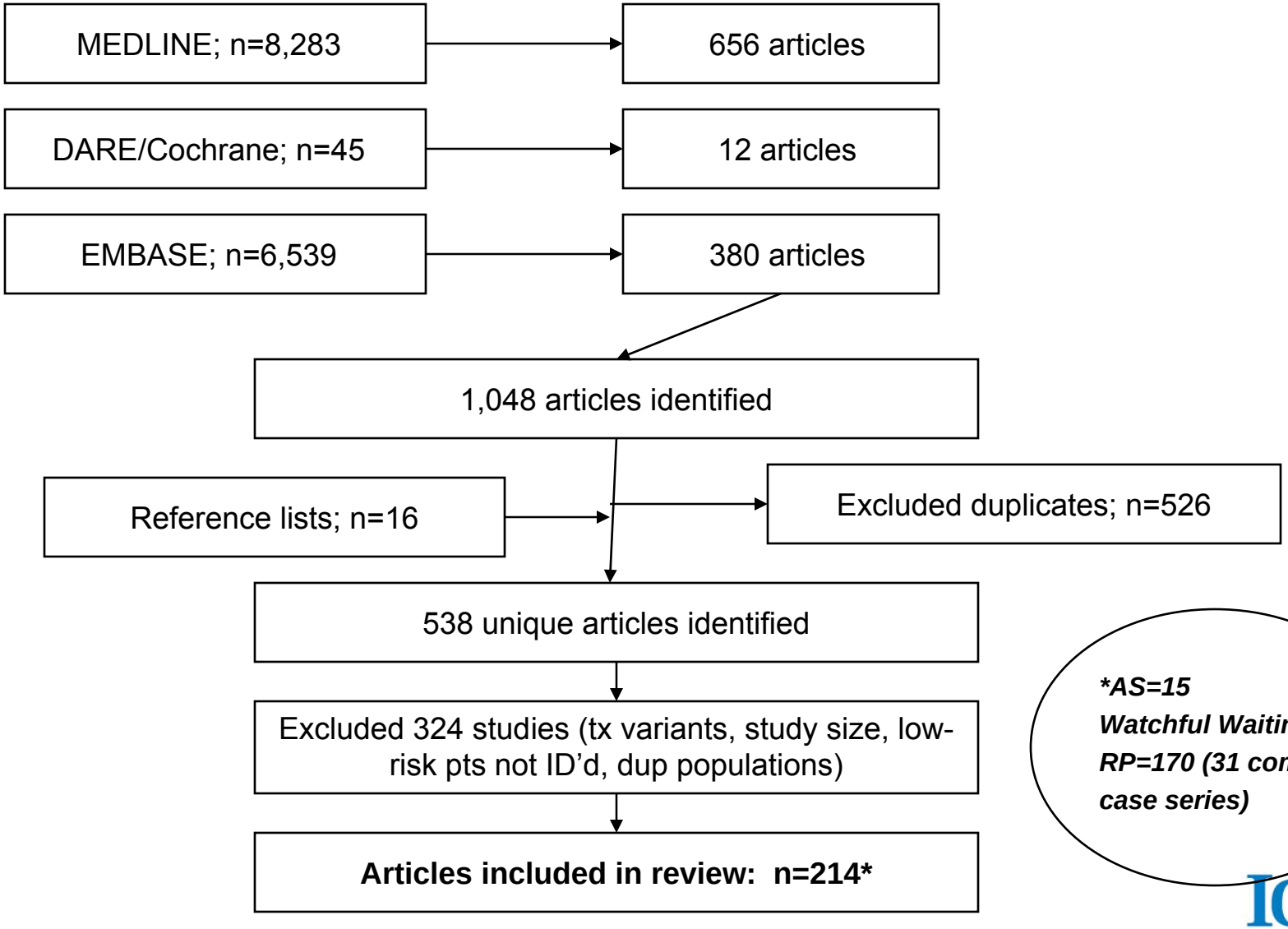
Outcomes Assessed

- Symptoms/Harms (RP):
  - Peri-operative:
    - Mortality
    - Major complications (hemorrhage, DVT/PE, systemic infection, MI/stroke, bowel injury)
    - Minor complications
  - Long-term:
    - Incontinence/leakage
    - Anastomotic stricture
    - ED

Outcomes Assessed

- Other (RP only):
  - LOS
  - Operative time
  - Blood loss
  - “Cath-in” time
  - + margins
  - Conversions (RALP/LRP to RRP)

Literature Search Results



***AS=15**
***Watchful Waiting=29**
RP=170 (31 comp, 139 case series)

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Evidence Quality

- Radical prostatectomy (comparative studies only)
  - 1 RCT, 23 w/contemporaneous controls, 7 w/historical controls
  - By type:
    - RRP vs. LRP: 17
    - RRP vs. RALP: 9
    - LRP vs. RALP: 5
  - No multi-center studies
  - Variable definitions and reporting (long-term SE, recurrence, complications)
  - Censored f/u in many cases
  - Highest-quality studies (RCT, matched comparisons) showed comparable outcomes by approach (Guazzoni 2006, Rozet 2007, Krambeck 2008)

Evidence Quality

- Active surveillance (n=15)
  - No RCTs or comparative studies (excluding older WW studies)
  - No data on urinary/sexual symptom progression
  - Variability in monitoring protocols
  - Variability in assessment frequency

Systematic Review Findings

- Overall Survival
  - AS (n=10): 77-100% at 5-8 years of f/u
  - Not reported in any RP comparative study
- Disease-Specific Survival
  - AS (n=12): 98-100% at 5-8 years of f/u
  - Not reported in any RP comparative study
- Limited evidence on RP vs. AS suggests no differences in survival
  - In contrast to observed differences for RP vs. WW (Bill-Axelson 2008)

Biochemical Freedom from Failure (RP Only)

- Measured in 10 RP comparisons
- No standard measurement algorithm
  - Not comparable to radiation studies employing algorithms based on PSA change
- Rarely expressed as K-M function
  - Shorter duration of f/u with newer techniques imparts significant bias

Initiation of Treatment (AS Only)

- Measured in 7 reports
- Proportion treated: 27% (range: 14-35% at median of 3.4-6.0 years of f/u)
- Approximately 2/3 treated due to clinical progression, 1/3 from patient choice
  - Progression most often based on Gleason increase on re-biopsy and/or measures of PSA velocity

Symptoms

- Active Surveillance:
  - Progression of urinary/sexual symptoms not measured in any report of modern AS cohort
  - Older WW data suggest prevalence of 40-50% for these symptoms (Steineck 2002)
    - Previous modeling effort used estimates for progression from non-prostate cancer populations (Bacon 2003, Andersson 2004)
  - Anxiety data for AS limited
    - Older WW data indicates moderate-high anxiety prevalent (30-40%) (Steineck 2002)
    - Appears to be correlated with advanced disease, however (Litwin 2002), and may not worsen over time (Arredondo 2008)

Harms

- Radical Prostatectomy:
  - Peri-operative mortality: only 3 deaths reported in ~9600 patients
  - Major surgical complications:
    - RRP (n=16): 5.5% (range: 0-28.6%)
    - LRP (n=16): 4.1% (range: 0-36.6%)
    - RALP (n=11): 2.7% (range: 0-7.8%)
  - Minor surgical complications:
    - RRP (n=16): 6.1% (0.3%-24.3%)
    - LRP (n=16): 9.8% (0-23.5%)
    - RALP (n=11): 6.3% (range: 0.5-15.1%)

Harms

- Radical Prostatectomy, Long-Term SE:
  - Anastomotic stricture:
    - RRP (n=7): 3.2% (0.4%-9.8%)
    - LRP (n=9): 1.9% (0.2-6.4%)
    - RALP (n=6): 1.7% (0-2.9%)

Harms

- Radical Prostatectomy, Long-Term SE:
  - Significant variability in methods to measure incontinence/ED, baseline continence/potency, and measurement timepoints
  - Incontinence (defined as pad use, among baseline continent, 12 mos)
    - RRP (n=4): 22.8% (range: 14.3-25.2%)
    - LRP (n=6): 33.6% (range: 9.6-50.3%)
    - RALP (n=2): 21.8% (range: 6.7-50.0%)
  - Short-term rates (3 mos) for all surgery types ranged from 37-80%

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Harms

- Radical Prostatectomy, Long-Term SE:
  - ED (among baseline potent, bilateral nerve-sparing, 12 mos)
    - RRP (n=5): 46.6% (range: 37.2-70.0%)
    - LRP (n=4): 42.8% (range: 30.2-47.0%)
    - RALP (n=3): 28.8% (range: 18.8-35.0%)
  - Short-term rates for all surgery types ranged from ~60-80%

Other Measures

- Radical Prostatectomy:
  - Open conversions rare (19 reported in ~5500 cases)
  - Nominally reduced LOS, blood loss, and cath-in time with RALP/LRP vs. RRP
  - Positive surgical margin rate similar for LRP and RRP:
    - Lower reported rate for RALP from small evidence base with heterogeneous results

Learning Curve

- Recognition of learning curve with RALP/LRP fairly common in comparative studies
- Threshold for completion of curve highly variable, however (range: 10-200 cases)
- Few studies explicitly compared outcomes during vs. following learning curve
  - Most excluded from consideration cases occurring during learning curve

Summary

- Modern AS protocols have yielded sparse data to date, particularly on symptom progression
- No evidence suggesting survival benefit for RP vs. AS (as opposed to WW)
- Relatively large set of comparative studies available for RP approaches
  - Generally low-quality comparisons, however
- Little data to distinguish RP by surgical approach:
  - Observed differences (e.g., blood loss, LOS, cath-in time) unlikely to have major clinical impact

Key Questions/Next Steps

- Criteria for exclusion of "flawed" studies
  - Exclude studies with f/u that differs by >10%
- Criteria for consideration of non-comparative case series
  - Consider *all* data equivalent to case series
- Incorporation of data from older WW literature
  - Examine baseline rates of continence/potency, data on progression
- Key elements of focus in final appraisal
- Other data, studies of interest?