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Surgery Provides Better Oncologic Outcomes than Radiation for the Treatment of Prostate Cancer

CON

*"It is not what you don't know that gets you into trouble,
It's what you know for sure, that just ain't so."*

—Mark Twain

MANY urologists seem to “know” that radical prostatectomy (RP) provides greater survival than radiotherapy (RT), and as a result there has been an increase in the performance of surgery for high risk prostate cancer in the last 5 years.¹ This hypothesis is supported by literature consisting of (flawed) retrospective studies.² Space does not allow me to address these studies in detail but virtually all of them would be characterized as providing a “low level of confidence” using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) Cochrane type approach.³ Many of these studies are prone to a huge risk of attribution bias because a death was classified “due to prostate cancer” if this diagnosis was listed on any of the top 3 lines of the death certificate.⁴ Since patients treated with RT are more likely to die of other causes, they are at greater risk for death to be attributed to prostate cancer even if they did not die of this disease. This risk is magnified by the large size of these population based studies (eg 20,000) such that an attribution bias error of 2% could translate into increased hazard ratios that would result in statistically significant differences. Also, many studies used SEER (Surveillance, Epidemiology and End Results) data that are unreliable for such comparative studies because before 2010 biopsy Gleason score was used for RT cases but pathological Gleason score was used for RP cases. Furthermore, accurate prostate specific antigen data were not available.⁵ Other reasons for doubting the usefulness of these studies are discussed in our recent critical analysis of this topic.³

Despite the many shortcomings of these population based studies, in a recent meta-analysis Wallis et al asserted that approximately 90% had a low risk of bias.² A careful review of these studies

reveals major differences between the patients treated with RP and those treated with RT (bias), thus completely discrediting their assertion and the conclusions of their study. Using a novel approach based on a respect for treatment with RT combined with androgen deprivation therapy (ADT), supported by level I evidence and accounting for various types of bias, we reached different conclusions than Wallis et al. Based on the most reliable studies comparing RP to RT with or without ADT, when men were treated in accordance with the current standard of care, the median difference in 10-year cause specific survival (CSS) was 1% (95% CI -2% to 7%, $p=0.24$).³ We concluded that this residual 1% CSS difference favoring RP over RT could easily be explained by failure to adjust for several factors associated with a worse outcome.³ We further concluded that the results with dose escalated image guided RT might be superior to those expected with RP for men with high risk prostate cancer, if long-term ADT was used in accordance to NCCN® guidelines.³

The only major trial establishing the efficacy of RP compared to “watchful waiting” showed that the benefits appeared to be limited to men younger than 65 years. In contrast, multiple phase III trials have shown that for men who need treatment the most, RT is highly beneficial, even for those with T3 disease and those older than 70 years. The fact that several studies have shown that older men would be expected to have more advanced disease than younger men supports the hypothesis that there may be unique biological interactions between ADT and RT in older men.³

In conclusion, although limited data from a single phase III trial suggest the benefits of RP exist only for men younger than 65 years, there is a robust body of phase III trials, dating back 30+ years, mostly populated by men older than 65 years, providing level I evidence of the benefit of RT.³ The best data, based on current standards of care, suggest that the 10-year CSS rates from prostate cancer are essentially identical following

RP and RT plus ADT.^{3,6} Given the higher 30, 60 and 90-day mortality rates, higher rates of erectile dysfunction, increased risk of incontinence and the lack of good evidence that RP improves survival compared to RT with or without ADT, I caution urologists against what they “know for sure” and confidently offering surgery as the “best

treatment” for men older than 65 years with high risk prostate cancer.³

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PRO

It is widely accepted that there is no significant difference in mortality outcome between surgery and radiotherapy, and that the net effect on quality of life of both treatments is comparable.¹ Both therapies are widely used for all risk categories of prostate cancer and substantial evidence suggests that provider preferences have a major impact on patient choice of treatment.² No meaningful randomized trial data exist to address this important question, although several attempts have been made to perform such a comparison.³ However, there are now 15 independent studies, of which 10 were published in the last 3 years, comparing the effectiveness of RP and RT using the propensity adjustment to correct for selection bias and other confounders. These studies have an important message for the relative effectiveness of these techniques.

Prostate cancer specific mortality (CSM) and overall survival (OS) outcomes of surgery and radiotherapy were evaluated in all 15 studies in a number of patients ranging from 453 to 66,492 (see table).^{4–10} After adjustment for known covariates, every study demonstrated improvement in CSM (HR 1.66–3.0) for patients treated with surgery as primary therapy. A benefit in OS was also noted after primary surgery in 8 studies (HR 1.5–1.7).

Zelevsky et al compared the outcome of RP and RT in 2,380 patients, and the hazard ratio for prostate cancer metastasis was 0.35 for RP vs RT.¹¹ This effect was seen most strikingly in the high risk group. Cooperberg et al performed a sensitivity

analysis on the degree to which unmeasured confounders would have to influence outcome and their observation was robust to 20 Kattan risk points, a substantial effect.⁴ Given that at a minimum grade, prostate specific antigen, stage, age and comorbidity were incorporated into the propensity adjustments, it is difficult to imagine an unmeasured confounder that would account for such a large difference in CSM, suggesting that unmeasured confounders are an unlikely explanation. In a similar population based study from Germany 12,740 patients underwent RP and 2,435 received RT (unpublished data). CSM was 1.97 times higher in the RT group, which was confirmed in a matched pair analysis.

Several population database analyses have recently addressed the long-term complications of surgery vs radiation. In a population based study Nam et al showed that at 5 years there were twice as many hospital admissions, 2.5 more hospitalizations lasting more than 1 day, and a much higher rate of open surgical procedures and rectal procedures.¹²

Summary of mortality results for RP vs RT from propensity analyses

References	No. Pts	CSM Favoring RP vs RT (HR)	OS Favoring RP vs RT (HR)
Cooperberg et al ⁴	7,538	2.1	
Kibel et al ⁵	10,249	1.5	1.8
Abdollah et al ⁶	68,685	1.8	
Shao et al ⁷	66,492	1.5	
Sooriakumaran et al ⁸	34,515	1.76	
Sun et al ⁹	67,087	0.4	0.66
Wallis et al ¹⁰	118,830	2.08	1.63