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The Comparative Oncologic Effectiveness of Available Management Strategies for Clinically Localized Prostate Cancer

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Introduction

Among cancer deaths in the U.S., prostate cancer ranks second to lung cancer with an estimated 27,540 deaths attributable to the disease in 2015.¹ Nonetheless, prostate cancer mortality rates continue to decline, and most men will die with prostate cancer rather than from it.² Therefore, the primary goal of modern prostate cancer treatment paradigms is to optimize the balance of predicted benefits associated with prostate cancer treatment against the predicted harms of therapy. However, given the limitations in the existing evidence as well as the significant tradeoffs posed by each treatment, there remain myriad challenges associated with individualized prostate cancer treatment decision-making.

Radical prostatectomy (RP), radiation therapy (RT), and active surveillance (AS) are all considered acceptable primary treatment options for men with localized prostate cancer. There remain few high quality comparative effectiveness data upon which clinical decisions may be based. This is, at least in part, due to a lack of randomized data directly comparing the effectiveness between, rather than within, major treatment groups. Furthermore, extrapolating data from existing randomized trials remains difficult owing to the stage-migration that occurred during the PSA era and perceived differences in both effectiveness and morbidity with contemporary as opposed to historical technologies. Another challenge is the substantial variation that exists in reporting clinical outcomes. Nevertheless, clinicians and patients are still faced with the decision of how to best proceed after a diagnosis of localized prostate cancer.

In this context, we summarize the existing comparative effectiveness evidence of treatments for localized prostate cancer with an emphasis on oncologic control. While we focus on the

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major treatment categories of RP, RT, and observation we also provide a review of emerging therapies such as cryotherapy and high-intensity frequency ultrasound (HIFU) particularly as it pertains to the efficacy of focal therapy in the primary treatment of prostate cancer.

Radical Prostatectomy

Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4)

The Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) is a randomized trial of RP versus watchful waiting in men with localized prostate cancer.³ The SPCG-4 was the first to publish a randomized intention-to-treat analysis comparing watchful waiting and RP using informative clinical endpoints such as overall and cancer-specific survival. Furthermore, the SPCG-4 offered the long-term follow-up necessary to characterize between-group differences in survival and employed rigorous study design methods such as blinded histopathological review. However, because this trial enrolled men predominantly during the pre-PSA era, nearly 90% of the 695 participants harbored palpable disease. This is in stark contrast to the distribution of local disease extent in contemporary series. Furthermore, there is little question that watchful waiting bears little resemblance to contemporary active surveillance protocols with close monitoring and intention to cure with disease progression. Nevertheless, a number of important observations regarding the comparative effectiveness of RP in the treatment of localized prostate can be made from the SPCG-4 data.

First, RP improves overall survival among men with localized prostate cancer compared to observation alone. While the initial report at a mean follow-up of 6.2 years did not demonstrate an overall survival benefit,³ the cumulative incidence of death from any cause at 18 years of follow-up was 56% in the RP group and 69% in the watchful waiting group, corresponding to a relative risk of death in the RP group of 0.71 (95% CI: 0.59, 0.86; $p<0.001$).⁴ The number needed to treat to prevent one death at 18 years of follow-up was 8, lower among men under the age of 65, comparing favorably to the breast cancer literature.⁵ Second, in addition to overall survival, RP improves cancer-specific survival among men with localized prostate cancer. The initial publication of the SPCG-4 revealed an absolute difference in prostate cancer specific mortality of 2% at 5 years and 6.6% at 8 years in favor of prostatectomy.³ By 18 years of follow-up, the absolute difference increased to 11%, corresponding to a relative risk of death from prostate cancer in the RP group of 0.56 (95% CI: 0.41, 0.77; $p<0.001$). Third, RP reduces the risk of metastatic disease and the need for androgen deprivation therapy. At 18 years after randomization, the use of hormone therapy was reduced by 25% (relative risk 0.49, $p=0.001$) and the incidence of metastatic disease was reduced by 12% (relative risk 0.57, $p=0.001$) in the RP group.⁴ While the overall survival benefit was only observed for men under 65 years of age, there was a significant reduction in the risk of metastatic disease (RR 0.68, $P<0.001$) and the need for hormone therapy (RR 0.60, $P<0.001$) among older men which may be an important indicator of disease burden. Taken together, these data confirmed the benefit of RP compared to watchful waiting in men with clinically localized prostate cancer and highlight the need for extended follow-up when studying the comparative effectiveness of prostate cancer therapy.

Radical Prostatectomy Versus Observation for Localized Prostate Cancer Trial (PIVOT)

In the Radical Prostatectomy Versus Observation for Localized Prostate Cancer Trial (PIVOT), 731 men with predominately screen-detected localized prostate cancer were randomized to either observation or RP. Unlike SPCG-4, PIVOT did not reveal an improvement in overall survival (hazard ratio, 0.88; [0.71 to 1.08]; $P=0.22$; absolute risk reduction, 2.9 percentage points) or prostate cancer specific survival (hazard ratio, 0.63; [0.36 to 1.09]; $P=0.09$; absolute risk reduction, 2.6 percentage points) for individuals randomized to RP at 10 years of follow-up, except in a subset of men with a PSA >10 ($P=0.004$).⁶ While the incidence of bony metastatic disease was lower in the RP group (4.7% versus 10.6%), these data suggest a null effect of RP on long-term overall and prostate cancer-specific survival.

SPCG-4 versus PIVOT

Why is there such a big difference in the conclusions of these two trials, especially in light of the fact that they are both similarly sized, randomized control trials evaluating RP versus no treatment among patients with clinically localized prostate cancer? First, the difference between SPCG-4 and PIVOT with respect to survival may not be as dramatic as it appears as PIVOT did not meet their pre-specified enrollment targets and, therefore, had limited statistical power to detect a significant difference in the primary endpoint. This is evidenced by the wide confidence intervals around overall and cancer-specific survival ([0.71 to 1.08] and [0.36 to 1.09] respectively). Second, unlike SPCG-4, PIVOT included more indolent cancers. In the PIVOT trial, 50% of men had clinical stage T1c versus only 12% of men in the SPCG-4 and the mean PSA for the SPCG-4 was 13 ng/mL versus 7.8 ng/dL in the PIVOT trial. This difference contributes to a lead time in PIVOT during which, by definition, no prostate cancer deaths occur and necessitates a comparatively longer follow-up for PIVOT before differences in survival would be expected. Third, in the PIVOT study, only 77% of patients allocated to RP actually underwent an RP compared to 94% in the SPCG-4 trial (6% were found to have lymph node involvement at the time of surgery and therefore did not undergo a RP). It is unclear to what extent this lower adherence to the randomized assignment in PIVOT affected the results as the authors of PIVOT have not published a per-protocol analysis. Lastly, the rate of death from all causes in PIVOT at 10 years appears to be quite high (48%, [354 of 731]), which raises important questions about the life expectancy of men enrolled in PIVOT and, ultimately, their ability to enjoy the possible long-term survival benefit conferred by definitive prostate cancer treatment. In contradistinction, the overall death rate at 10 years of follow-up the in SPCG-4 trial was only 27% (189 of 695).

Taken together, direct comparisons between PIVOT and SPCG-4 are challenging, and underscore the importance of contextualizing the study question before making inferences about available data. Whereas the SPCG-4 demonstrates a clear benefit of RP over the long-term in a predominantly white Scandinavian population of patients with clinically palpable yet localized prostate cancer, the PIVOT trial demonstrates a null effect of RP over the short-term in a predominantly older, more comorbid population of American patients with clinically indolent disease. These are two very important, but altogether different, questions that inform contemporary surgical practice for localized prostate cancer.

Open versus Robotic Prostatectomy

Laparoscopic and robotic approaches to RP have amassed increasing popularity over the last two decades secondary to purported improvements in perioperative and functional outcomes. However, despite the rapid diffusion of minimally invasive techniques among urologists worldwide, long-term data on oncologic endpoints, such as overall and cancer specific mortality, are not yet available. As a result, surrogate measures of oncologic efficacy such as lymph node yield, positive margins, use of adjuvant therapy, and biochemical free survival have been extensively studied.

Perhaps the most common proxy for oncologic efficacy is biochemical free survival (BFS). In a retrospective analysis of 1384 patients treated between 2001 and 2005, the actuarial BFS at 7 years of follow-up for robotic RP was 81%.⁷ In patients who recurred, the median time to recurrence was about 20 months. In a similar prospective analysis of 184 patients treated with robotic RP between 2003 and 2005, the 7 year actuarial BFS was likewise 81%.⁸ These numbers are comparable to those published in both pure laparoscopic^{9,10} and open cohorts.¹¹

Another surrogate measure for oncologic efficacy is positive surgical margin (PSM) rates. However, variation in margins rates may be due to myriad factors unrelated to the surgical approach itself such as extent of disease, surgeon skill, pathologic processing, and surgical artifact.¹² Nevertheless, several studies have evaluated the comparative effectiveness of robotic, laparoscopic, and open approaches on the rate of PSM and the results are mixed; while some studies demonstrate an improvement in the rate of PSM with robotic RP, others demonstrate no difference.^{13–16} In a study comparing PSM rates between 200 open and 200 robotic RPs, the PSM rate for robotic RP was substantially lower than the open cohort (15% versus 35%).¹³ Even among T2 tumors, the PSM rate varied substantially (9% for robotic versus 24% for open). However, the open patients clearly had a preponderance for high risk disease (higher PSA, clinical stage, and Gleason score) which undoubtedly confounds the comparison. Given the lack of high-quality long-term data using meaningful measures of oncologic efficacy, the comparative effectiveness of minimally invasive and open approaches with respect to long term cancer control remains unknown.

Radiation Therapy

Randomized Clinical Trials Comparing Radiation Versus Prostatectomy

Only one randomized clinical trial (RCT) has evaluated the comparative effectiveness of RP, RT, and AS – the results of which have not yet been published.¹⁷ To date, few published data have directly compared RT to RP in a randomized fashion.^{18,19} In a study of 106 patients with clinical stage T1 or T2 disease, RP was more effective in preventing progression, recurrence, or distant metastatic disease.¹⁸ Treatment failure was defined as two consecutive rises in prostatic acid phosphatase levels or the development of metastatic disease. After 5 years, failure was observed in 39% for RT compared to 14% of RP patients. Only two patients in the RP group were diagnosed with metastatic disease compared to 14 in the RT group.

In a separate RCT of 95 patients, the 10 year biochemical-free, cancer-specific, and overall survival rates favored RP compared to RT.¹⁹ At a median followed up of 102 months, BFS for the RP group was 76.2% versus 71.1% for the RT group; cancer-specific survival of the RP group was 85.7% versus 77.1% for the RT group; and overall survival was 67.9% in the RP group and 60.9% in the RT group. These differences failed to achieve statistical significance; furthermore, both of these trials were small and performed in the pre-PSA era and before substantial technical refinements to both RP and RT which markedly limits the extrapolation of these data into modern clinical practice.

Observational Cohort Studies Comparing Radiation to Prostatectomy

Several high-quality observational cohort studies have demonstrated similar rates of BFS among patients treated with RP and RT.^{20,21} However, the use of BFS as an oncologic endpoint to compare treatments is problematic for myriad reasons. First, there is tremendous variation in the definition of BFS. Second, variation in post-treatment PSA kinetics may also impact observed differences in rates of BFS after RP and RT because the cytotoxic effects of RT may take several months or years and it does not eliminate all prostatic sources of PSA. Lastly, the differential use of androgen deprivation therapy (ADT), which is especially common among high-risk radiation patients, may delay time to biochemical progression.

Due to these limitations, several studies have attempted to evaluate the long-term comparative effectiveness of surgery and radiation for the treatment of clinically localized prostate cancer. In a large series of over 2300 patients with clinical stage T1-T3 prostate cancer treated at Memorial Sloan Kettering Cancer Center, treatment with RP was associated with significant reduction in the risk of metastatic disease (HR 0.35, $p < 0.001$) and cancer-specific mortality (0.32, $P < 0.001$) compared with RT.²² In a separate study of 1847 high-risk patients with localized prostate cancer at Mayo Clinic and Fox Chase Cancer Center, the authors likewise demonstrated improved long-term survival among patients undergoing RP as compared to RT.²³ The 10 year overall survival rate of RP patients was 77% versus 67% following RT plus ADT versus 52% with just RT alone.

Population Based Studies Comparing Radiation To Prostatectomy

To address concerns that treatment effects may differ in the community compared to what is observed in tertiary care centers, several population-based analyses have evaluated the comparative effectiveness of RT and RP. In a large population based trial of over 34,000 Swedish men with localized prostate cancer, the risk of prostate cancer specific mortality was higher among RT patients as compared to RP patients (HR 1.76 [95% CI: 1.49 to 2.08]).²⁴ A similar study using data from CaPSURE likewise found a higher prostate cancer specific mortality rate after adjusting for age and disease risk (HR 2.21; 95% CI: 1.50-3.24)²⁵ as have several SEER studies.²⁶⁻²⁸ In a study of over 1500 men with 15 years of follow-up from the Prostate Cancer Outcomes Study, RP was associated with a statistically significant overall (HR 0.60; 95%CI 0.53, 0.70) and disease specific (HR 0.35; 95%CI 0.26, 0.49) survival advantage.²⁹

However, well known biases frequently confound the interpretation of observational comparative-effectiveness studies. Treatment selection bias, for example, could skew

estimates of survival differences in favor of surgery. Even with rigorous case-mix adjustment using propensity scores or instrumental variable analysis, other unmeasured confounders may drive spurious survival estimates. By way of example, one of the studies comparing RP to RT demonstrated differences in non-prostate cancer mortality between treatments even after adjustment which suggests that the RT group had poorer prognosis at baseline.²⁴

Intensity Modulated Radiation Therapy and Proton Beam Therapy

Similar to the rapid diffusion of minimally invasive techniques in the surgical realm, emerging technologies such as intensity modulated radiation therapy (IMRT) and proton beam therapy have been rapidly adopted despite the lack of long-term data supporting either superior oncologic efficacy or reduction in treatment-related morbidity. While there is some evidence that novel radiation therapies may improve the dose distribution with higher doses delivered locally to the tumor thereby preserving surrounding healthy tissues, these assertions remain unproven in studies to date.^{30–35} While there are no RCTs comparing proton therapy to conventional RT or brachytherapy, there is one randomized trial that evaluated prostate cancer control after high dose radiation boosting with proton beam therapy.³⁶ After 8 years of follow-up, combination therapy was better than conformal therapy alone (OR 1.88; 95% CI: 1.04, 3.41). Two other nonrandomized phase II clinical trials^{37,38} and several cases series from centers of excellence have reported favorable clinical outcomes among patients treated with proton beam therapy.^{39,40} Similarly, no clinical trials compared the effects of clinical outcomes after IMRT vs. other treatments for localized prostate cancer. A few case-series reported better biochemical –free survival after IMRT compared to conformal radiation alone.^{41,42}

Brachytherapy

Brachytherapy remains a therapeutic option for properly selected men with low and low-intermediate risk clinically localized prostate cancer. Two different RCTs comparing RP to brachytherapy have been closed prematurely due to poor accrual.^{43,44} In a separate small randomized trial comparing brachytherapy to RP in men with clinical stage T1c/T2a disease, brachytherapy achieved comparable 5 year biochemical free survival rates (91.0% for RP and 91.7% for brachytherapy).⁴⁵ However, the small number of patients (N=200) and the short follow-up limit the conclusions regarding long-term oncologic efficacy. While other nonrandomized comparisons between brachytherapy and RP have been published,^{46–49} robust experimental data with sufficiently long follow-up remain lacking in the prostate cancer literature.

Ablative Therapy and Focal Therapy

While surgery and radiation each appear to provide excellent long-term oncologic control, these treatments are accompanied by significant risk of side effects that profoundly affect quality of life. Similarly, the appeal of active surveillance is offset by the lack of validated mechanisms for the identification of appropriate candidates, patient anxiety regarding the implications of delayed treatment for long-term cancer control, and the repeat biopsies currently required to monitor for progression. Consequently, some men with localized prostate cancer are turning to alternative therapies, such as high-intensity frequency

ultrasound (HIFU) and cyroablation, which may offer the promise of curative intent therapy with lower rates of treatment related morbidity.^{50,51}

High Intensity Frequency Ultrasound

Over the last decade, HIFU has been used in the treatment of many different solid-organ tumors, such as breast, pancreas, liver, and kidney.^{52–54} However, the most widely used indication for this technology remains prostate cancer. Introduced in the early 1990s,⁵⁵ HIFU was initially used as primary treatment in patients who were not acceptable surgical candidates or as salvage therapy for patients with biochemically recurrent disease after radiation.^{56–59}

The challenge of interpreting the reported oncologic efficacy of HIFU lies in the lack a universal consensus on the definition of treatment failure. In the HIFU literature, it is customary to report negative biopsy rates as a surrogate measure of oncologic efficacy; yet, whether biopsy is uniformly performed and when, varies tremendously between studies. While the early studies of HIFU demonstrated promising five-year DFS between 66% and 78%,^{56,60,61} the impact of the lack of standard definitions for treatment failures becomes evident in more contemporary studies. In a report of 140 HIFU-treated men with stage T1-T2 prostate cancer, a PSA of less than 15 ng/mL, and a Gleason score less than 7, the stricter criteria for treatment failure (PSA according to the Phoenix criteria,⁶² a positive biopsy, or salvage therapy) lead to comparatively lower success rates. In this study, the 5- and 7-year disease-free survival rates were 66% and 59%, respectively.⁶³ Because the mean follow-up was only 6 years in this study, long-term follow-up is necessary to characterize how these rates will evolve over time.

In light of the lack of long-term data regarding the oncologic efficacy of HIFU for the primary treatment of localized prostate cancer, it is our opinion that this therapy should be used only in the setting of a clinical trial or reserved for surgically-ineligible, medically-comorbid men with low- to intermediate-risk disease who refuse active surveillance or radiation.

Cryotherapy

Cryoablation appears to have reasonable oncologic efficacy for patients with clinically localized prostate cancer. In an RCT comparing cryoablation to RT in 244 men, no difference was noted in the 3-year biochemical free survival rates between the two groups (76% in both groups).⁶⁴ In a separate multi-institutional trial of whole gland cryotherapy, 81% of patients had a PSA nadir of less than 0.4 ng/ml and 78% of those with low risk disease (Gleason 7 or less and a PSA less than 10 ng/mL) were free of biochemical progression at 12 months.⁶⁵ In a single-institution long-term analysis of 590 patients, 7-year actuarial BFS for low risk patients was approximately 61%.⁶⁶ However, not all data support the notion that cryoablation and radiation are equivalent, especially in the setting of high-risk disease. Data from an RCT in which 62 men with clinical stage T2c-T3b disease were randomized to either cryoablation or RT, cryoablation was associated with a substantially lower 8-year biochemical disease-free survival rate (17% versus 59.1%, $P=0.01$). While this

trial was a single center study with small numbers due to poor accrual, it raises important questions about the comparative oncologic efficacy of cryoablation for high-risk patients.

The Future of Ablative Therapy

While energy ablative therapies represents an exciting forefront of prostate cancer treatment, the limited experience and immature follow-up necessitate the publication of long-term cancer control rates before widespread implementation. Furthermore, while it seems intuitive that focal therapy lowers the likelihood and severity of treatment related morbidity, this must be empirically validated through the systematic collection of patient reported quality of life outcomes.

Hormone Therapy

Studies that advocate for the use of primary androgen deprivation therapy are retrospective, underpowered, have short-term follow-up, and lack critical assessment of the comparative harms of ADT alone.⁶⁷ Furthermore, the preponderance of evidence from multiple large population based studies demonstrates no improvement, and in some causes worse survival, with the use of primary ADT.^{68–71} As a result, guidelines from both the NCCN and the AUA both recommend against the use of primary androgen deprivation therapy.^{72,73}

Conclusions

Based upon the current state of the literature, no one therapy can be heralded as the preferred method of treating localized prostate cancer. For young men with high risk disease, RP offers a long-term survival benefit compared to observation alone. Nonetheless, whether these men would enjoy the same survival advantage were they to undergo radiation therapy remains unknown. The results from the forthcoming Prostate Testing for Cancer and Treatment (ProtecT) trial, which compares radical prostatectomy, radiation therapy, and active surveillance, are highly anticipated.

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