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Seminar article

The comparative oncologic effectiveness of available management strategies for clinically localized prostate cancer

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Abstract

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. In this review, we summarize the existing comparative effectiveness evidence of treatments for localized prostate cancer with an emphasis on oncologic control. While we focus on the major treatment categories of radical prostatectomy, radiation therapy, and observation, we also provide a review of emerging therapies such as cryotherapy and high-intensity frequency ultrasound (HIFU). © 2016 Elsevier Inc. All rights reserved.

Keywords: prostate cancer; prostatectomy; radiation therapy; active surveillance; comparative effectiveness; oncologic efficacy

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 goal of modern prostate cancer treatment 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 are only a 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 prostate-specific antigen (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. Although we focus on the 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).

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 vs. watchful waiting

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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 AS 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. Although 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, and even lower among men younger than 65 years, 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 (ADT). At 18 years after randomization, the use of hormone therapy was reduced by 25% (relative risk [RR] = 0.49; $P = 0.001$) and the incidence of metastatic disease was reduced by 12% (RR = 0.57; $P = 0.001$) in the RP group [4]. Although the overall survival benefit was only observed for men younger than 65 years, 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 with 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 vs. Observation for Localized Prostate Cancer Trial (PIVOT)

In the Radical Prostatectomy vs. 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 [HR] = 0.88; [0.71–1.08]; $P = 0.22$; absolute risk reduction, 2.9% points) or prostate cancer-specific survival (HR = 0.63; [0.36–1.09]; $P = 0.09$; absolute risk reduction, 2.6% 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]. Although the incidence of bony metastatic disease was lower in the RP group (4.7% vs. 10.6%), these data suggest a null effect of RP on short-term overall and prostate cancer-specific survival.

SPCG-4 vs. PIVOT

Why is there such a big difference in the conclusions of these 2 trials, especially in light of the fact that they are both similarly sized, randomized control trials evaluating RP vs. 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 ([0.71–1.08] and [0.36–1.09], respectively). Second, unlike SPCG-4, PIVOT included more indolent cancers. In the PIVOT trial, 50% of men had clinical stage T1c vs. only 12% of men in the SPCG-4 and the mean PSA for the SPCG-4 was 13 vs. 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 with 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

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