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European Association of Urology

Platinum Priority – Review – Prostate Cancer
Editorial by XXX on pp. x–y of this issue

Survival and Complications Following Surgery and Radiation for Localized Prostate Cancer: An International Collaborative Review

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Article info

Article history:
Accepted May 30, 2017

Associate Editor:
Giacomo Novara

Keywords:
Prostatic neoplasms
Mortality
Radiotherapy
Adverse effects
Prostatectomy
Comparative effectiveness research
Brachytherapy
Quality of life

Abstract

Background: Evaluation of treatment options for localized prostate cancer (PCa) remains among the highest priorities for comparative effectiveness research. Surgery and radiotherapy (RT) are the two interventions most commonly used.
Objective: To provide a critical narrative review of evidence of the comparative effectiveness and harms of surgery and RT in the treatment of localized PCa.
Evidence acquisition: A collaborative critical narrative review of the literature was conducted.
Evidence synthesis: Evidence to clearly guide treatment choice in PCa remains insufficient. Randomized trials are underpowered for clinically meaningful endpoints and have demonstrated no difference in overall or PCa-specific survival. Observational studies have consistently demonstrated an absolute survival benefit for men treated with radical prostatectomy, but are limited by selection bias and residual confounding errors. Surgery and RT are associated with comparable health-related quality of life following treatment in three randomized trials. Randomized data regarding urinary, erectile, and bowel function show few long-term (>5 yr) differences, although short-term continence and erectile function were worse following surgery and short-term urinary bother and bowel function were worse following RT. There has been recent recognition of other complications that may significantly affect the life trajectory of those undergoing PCa treatment. Of these, hospitalization, the need for urologic, rectoanal, and other major surgical procedures, and secondary cancers are more common among men treated with RT. Androgen deprivation therapy, frequently co-administered with RT, may additionally contribute to treatment-related morbidity. Technological innovations in surgery and RT have shown inconsistent oncologic and functional benefits.
Conclusions: Owing to underpowered randomized control studies and the selection biases inherent in observational studies, the question of which treatment provides

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http://dx.doi.org/10.1016/j.eururo.2017.05.055

better PCa control cannot be definitively answered now or in the near future. Complications following PCa treatment are relatively common regardless of treatment approach. These include the commonly identified issues of urinary incontinence and erectile dysfunction, and others including hospitalization and invasive procedures to manage complications and secondary malignancies. Population-based outcome studies, rather than clinical trial data, will be necessary for a comprehensive understanding of the relative benefits and risks of each therapeutic approach.

Patient summary: Surgery and radiotherapy are the most common interventions for men diagnosed with prostate cancer. Comparisons of survival after these treatments are limited by various flaws in the relevant studies. Complications are common regardless of the treatment approach.

1. Introduction

For three decades, management options for patients with clinically localized prostate cancer (PCa) have remained the same: surgery, radiotherapy, and observation. Many men, particularly those who are older or have low-risk PCa, will not benefit from active intervention [1]. For men with long life expectancy (>10 yr), treatment is recommended for those with intermediate- or high-risk PCa [2]. Both surgery and radiotherapy (now usually in combination with androgen deprivation therapy, ADT) have been used in the treatment of PCa for more than 100 yr. While other treatments such as high-intensity frequency ultrasound and cryotherapy are gaining prominence, the volume of evidence for intermediate- and long-term outcomes remains insufficient to guide treatment decision-making. Accordingly, these treatments are not routinely recommended in clinical practice guidelines [2].

Without significant supportive evidence, surgery and radiotherapy (generally in combination with ADT) have been advocated as having similar oncologic efficacy. Thus, treatment counseling and decision-making have been complex and predominately centered on the risks of urinary incontinence and erectile dysfunction and other radiation-specific side effects (and increasingly the side effects of ADT as we have become aware of them in the past decade). The importance of localized PCa management is highlighted by its selection by the Institute of Medicine as one of the top 25 priorities for comparative effectiveness research [3]. In the past few years, a significant body of literature assessing survival and complications following treatment of localized PCa has emerged. In this collaborative narrative review, we summarize historical and contemporary data evaluating survival outcomes and complications following radical prostatectomy and radiotherapy in the treatment of clinically localized PCa, including consideration of the role and toxicity of ADT co-administered in most modern radiotherapy regimes.

2. Evidence acquisition

Medline was systematically searched from inception until December 2016 using the following terms: "radical prostatectomy", "radiotherapy", "brachytherapy", "survival", "complications", and "outcomes", along with free-text, related, derivative, and exploded terms. The lead author compiled a proposed bibliography and manuscript framework that was iteratively revised by all co-authors. Following agreement on the manuscript structure, the first and senior authors drafted this narrative review that was critically revised by all co-authors. The final manuscript represents the consensus of the authors.

3. Evidence synthesis

3.1. Oncologic outcomes in PCa research

Many cancer-related outcomes have been used in comparative effectiveness studies of PCa treatments, including biochemical recurrence (BCR), clinical recurrence, metastasis, PCa-specific mortality, and overall mortality. All-cause (overall) mortality is the most reliable endpoint of any oncology study and, according to the US Food and Drug Administration, is the preferred endpoint owing to its precision and lack of ascertainment bias [4]. Previous work has shown that PCa may be reliably ascertained as a cause of death from administrative records [5]. Thus, PCa-specific survival is an alternative outcome that may more directly assess the oncologic efficacy of PCa therapies.

BCR is the outcome most commonly used in studies of PCa treatment efficacy as it develops relatively early following treatment [6]. While BCR is an important clinical event, most notably as it triggers further therapy with significant costs and quality-of-life (QoL) detriments [7–9], it is limited as a meaningful research outcome. First, approximately 10% of men with BCR will develop clinical progression [10], and <5% at 5 yr will ultimately die of the disease [10]. Thus, BCR is a poor surrogate measure for survival. Second, innumerable definitions of BCR exist. A systematic review of the literature in 2007 identified 53 different definitions of BCR following radical prostatectomy and 99 different definitions of BCR following radiotherapy [11], making it difficult to compare outcomes between studies. Finally, given the intrinsically different definitions of BCR for patients treated initially with surgery and radiotherapy, the use of BCR to compare outcomes following treatment with the two modalities is inherently problematic. Both the Phoenix criterion and ASTRO criteria as a definition of BCR systematically overestimate BCR-free survival for patients following radical prostatectomy [12]. Furthermore, Lee et al [13] showed that among men with comparable 5-yr risks of BCR, those treated with

Please cite this article in press as: Wallis CJD, et al. Survival and Complications Following Surgery and Radiation for Localized Prostate Cancer: An International Collaborative Review. Eur Urol (2017), http://dx.doi.org/10.1016/j.eururo.2017.05.055