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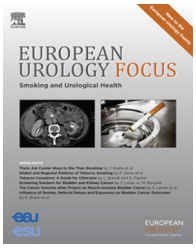

Platinum Priority – Review – Prostatic Disease

Comparative Oncologic and Toxicity Outcomes of Salvage Radical Prostatectomy Versus Nonsurgical Therapies for Radiorecurrent Prostate Cancer: A Meta–Regression Analysis

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Article info

Article history:
Accepted September 8, 2015

Associate Editor:
James Catto

Keywords:
Brachytherapy
Cryotherapy
High-intensity focused ultrasound
Prostate cancer
Radical prostatectomy
Salvage therapy

Abstract

Context: In the absence of randomised controlled trials comparing the oncologic, toxicity, and functional outcomes of salvage radical prostatectomy (SRP), salvage high-intensity focused ultrasound (SHIFU), salvage brachytherapy (SBT), and salvage cryotherapy (SCT), controversy exists as to the optimal salvage modality in radiorecurrent prostate cancer.
Objective: We carried out a meta–regression analysis to determine whether there is a difference in oncologic, toxicity, and functional outcomes using data from original publications of salvage modalities in the postradiation setting.
Evidence acquisition: We performed a systematic review of PubMed/Medline citations according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement. We included 63 articles in the analysis (25 on SRP, 8 on SHIFU, 16 on SCT, 14 on SBT).
Evidence synthesis: Median values of the following variables were extracted from each study: patient age, length of follow-up, prostate-specific antigen (PSA) before radiotherapy (RT), PSA before salvage therapy, Gleason score before RT, and time interval between RT and salvage therapy. Functional, toxicity, and oncologic outcomes were measured according to rates of impotence, incontinence, fistula formation, urethral strictures, and biochemical recurrence. Meta–regression adjusting for confounders found no significant difference in oncologic outcomes between SRP and nonsurgical salvage modalities. SBT, SCT, and SHIFU appeared to have better continence outcomes than SRP. No significant difference in toxicity outcomes between modalities was found, although limitations such as reporting, selection, and publication bias and between-study heterogeneity must also be considered with these conclusions.
Conclusions: Oncologic outcomes are comparable for SRP and all three nonsurgical salvage modalities. We found no significant differences in toxicity outcomes among modalities; however, SRP appears to be associated with worse rates of urinary incontinence than SBT, SCT, and SHIFU.
Patient summary: We performed a meta–regression analysis to compare oncologic, functional, and toxicity outcomes between salvage radical prostatectomy and nonsurgical salvage modalities. Oncologic and toxicity outcomes appear to be similar; however, all nonsurgical salvage modalities may be associated with better continence outcomes.

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http://dx.doi.org/10.1016/j.euf.2015.09.004

1. Introduction

For more than two decades, external-beam radiation therapy (RT) and low-dose-rate brachytherapy have been considered standard practice for the treatment of patients with clinically localised low-risk prostate cancer (PCa). Over the years, technological advances in this field have seen changes in the delivery of RT. The integration of various forms of image-guided RT for external-beam RT and brachytherapy and delivery with intensity-modulated RT have enabled accurate dose escalation to improve outcomes and reduce toxicity [1]. Radiobiological models have also indicated that PCa cells are more sensitive to doses delivered in larger fraction sizes than in smaller frequent doses [2]. Our understanding of this has been critical in the introduction and evolution of high-dose-rate brachytherapy, stereotactic body RT, and proton beam therapy. The introduction of higher radiation doses in addition to the use of adjuvant or neoadjuvant androgen deprivation therapy (ADT) have led to improved outcomes and thus to the hypothesis that this combination would likely produce additive improvements [3]. Even in the current era of dose-escalated RT for PCa and its combination with ADT, biochemical recurrence (BCR) is not uncommon and occurs in approximately 20–30% of patients [4].

According to European and British urologic guidelines, therapeutic options in patients with BCR after primary RT can include salvage radical prostatectomy (SRP), salvage high-intensity focused ultrasound (SHIFU), salvage cryotherapy (SCT), and salvage brachytherapy (SBT). These guidelines, however, advise that strong recommendations regarding the choice of any of these techniques cannot be made, as the available evidence for these treatment options is of very low quality; there are currently no randomised trials to compare the different modalities of salvage treatment in terms of oncologic, functional, and toxicity outcomes. The majority of available data come from single- or multi-institutional retrospective or prospective studies with short to intermediate follow-up. The decision of which modality to use is based largely on institutional practice and the availability of a particular technology rather than high-quality evidence. Evaluating the relative effectiveness of various salvage treatments in terms of relative cancer control and treatment-related morbidity has proved challenging. This is because of differing treatment-specific definitions of BCR, a lack of a standardised reporting system for toxicity outcomes, and large heterogeneity between studies regarding duration of follow-up, patient demographics, tumour risk profiles in terms of prostate-specific antigen (PSA) value and Gleason score, and interval between RT and salvage therapy. To date, the only studies attempting to compare these modalities have been systematic reviews [5–7].

To help inform further discussion on this topic, we carried out a meta–regression analysis to compare treatment biochemical failure rates, functional outcomes, and toxicity among the different available salvage options for radiorecurrent disease. Our primary interest was to compare reported outcomes between the most commonly reported salvage modality, SRP, and nonsurgical modalities.

2. Evidence acquisition

2.1. Search strategy and selection criteria

A systematic review of the literature was conducted using PubMed/Medline electronic databases. The search was restricted to English-language articles from January 1, 1994, to December 31, 2014. Search terms included *prostate cancer recurrence, prostate salvage therapy, radio-recurrent prostate cancer, local salvage treatment, SRP, SCT, SBT*, and *SHIFU*. We combined the search terms *prostate cancer recurrence* with *SHIFU, SRP, SCT*, or *SBT* for four separate searches.

2.2. Inclusion criteria

All authors participated in the design of the search strategy and inclusion criteria. Our procedure for evaluating records identified during the literature search followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) criteria. We included only original articles involving salvage therapy in the postradiation setting. Eligibility criteria for selecting studies included a diagnosis of nonmetastatic recurrent PCa after primary RT. All studies included in this analysis used the American Society for Radiation Oncology (ASTRO) or Phoenix definition of *biochemical recurrence* to identify BCR in patients following primary RT. The absence of nodal or bone metastases was evaluated in most cases using bone scintigraphy or pelvic magnetic resonance imaging to ensure local recurrence only. Eligibility criteria also included reporting of oncologic outcomes in terms of BCR rates, reporting comprehensively on functional outcomes in terms of incontinence and impotence using standardised and validated questionnaires, and reporting toxicity outcomes in terms of fistula and urethral stricture formation. In the included studies, recurrent PCa was diagnosed by either transrectal ultrasound–guided or template prostate biopsies prompted by a rise in PSA defined as recurrence of disease according to the ASTRO or Phoenix definition of BCR. Details as to the number of biopsy cores undertaken and the percentage of cores positive for cancer were not available. Any studies commenting on salvage treatments whereby the primary form of therapy was not RT were excluded from the analysis. The final list of included articles was selected with the consensus of all collaborating authors verifying that the articles met the inclusion criteria.

2.3. Outcomes

The main oncologic outcome of interest was BCR. For a pragmatic approach, we used each study's predefined criteria for biochemical relapse, recognising the lack of consistency of these definitions within and across treatment types. Other end points that determine oncologic efficacy, such as PCa-specific mortality, overall survival, progression to metastases, or extent of follow-up positive biopsies after salvage treatment, were scarcely reported in the literature and thus were not considered. We chose to