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EUO Collaborative Review – Prostate Cancer

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Optimizing the Timing of Salvage Postprostatectomy Radiotherapy and the Use of Concurrent Hormonal Therapy for Prostate Cancer

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Abstract

Context: Currently, salvage radiotherapy (SRT) is the only known curative intervention for men with recurrent disease following prostatectomy. Critical issues in the optimal selection and management of men being considered for SRT include the threshold prostate-specific antigen (PSA) value at which to initiate treatment (ie, pre-SRT PSA) and the role of concurrent hormonal therapy (HT).
Objective: To review the published evidence pertaining to the optimal timing for SRT and the role of concurrent HT.
Evidence acquisition: MEDLINE (via PubMed), EMBASE, the Cochrane Central Register of Controlled Trials, and guideline statements from professional organizations were queried from January 1, 2000 through January 10, 2018.
Evidence synthesis: Thirty-three independent reports, including two randomized trials evaluating HT with SRT, were identified. Retrospective data suggest that SRT initiation at lower pre-SRT PSA levels is associated with better clinical outcomes. Prospective data suggest an overall survival benefit with concurrent HT that manifests during long-term follow-up, with the caveat that hypothesis-generating subgroup analyses suggest that this benefit may be limited to patients with higher pre-SRT PSA levels. Patients with adverse risk factors, such as Gleason grade group 4–5 disease, are likely to benefit the most from earlier SRT initiation and/or the use of HT.
Conclusions: Given the limitations of the available data, it is imperative that physicians participate in shared decision-making, with the recommendation tailored for each man's desire to maximize oncologic benefit (with a risk of overtreatment) versus potential quality-of-life optimization (with a risk of undertreatment). Within that framework, a significant body of retrospective data supports initiation of SRT at low pre-SRT PSA values, without an arbitrary absolute threshold. Prospective data suggest a benefit of HT, but this benefit may be greatest in patients with a pre-SRT PSA that is higher than the typical level in most patients receiving "early" SRT. Further research is necessary before absolute recommendations can be made.
Patient summary: Two ways to potentially improve outcomes following salvage radiotherapy for prostate cancer that recurs after prostatectomy are to start treatment at a lower prostate-specific antigen level and to use concurrent hormonal therapy. Our review suggests that the available evidence is imperfect, but highlights that both measures are likely to improve clinical outcomes in general, but perhaps not uniformly and/or consistently for all patients. Physician-patient shared decision-making and further research are critical.

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1. Introduction

Prostate cancer (PCa) is the second leading cause of cancer-related death in the USA [1] and the third leading cause of cancer-related death in Europe [2]. Among men who ultimately die from their PCa, nearly 50% have potentially curable, localized disease at diagnosis that ultimately recurs after upfront treatment [3]. Therefore, effective management of men with biochemically recurrent PCa is integral in ultimately minimizing PCa-specific mortality (PCSM). Nearly 30% of men undergoing radical prostatectomy (RP) will ultimately experience a biochemical recurrence (BCR), defined as two consecutive prostate-specific antigen (PSA) levels >0.2 ng/ml [4,5]. In such patients, the only known curative intervention is salvage radiotherapy (SRT), which—on the basis of compelling but retrospective data—can offer a relative reduction in PCSM of up to 68% [6]. Unfortunately, patterns of care data indicate that SRT utilization rates can be as low as 42% among patients with PSA >0.2 ng/ml after RP [7]. This underutilization is reflective of a mix of practice philosophies that place varying weight on toxicity and oncologic benefit [8]. Critical issues in the optimal selection and management of men being considered for SRT include the threshold PSA value at which to initiate treatment (ie, pre-SRT PSA) and the role of concurrent hormonal therapy (HT). In this systematic review, we explore the rationale for and evidence pertaining to (1) the optimal timing for SRT and (2) the role of concurrent HT. We emphasize that further research is desperately needed to improve the efficacy of SRT and lessen the burden of PCSM among men with BCR after RP.

2. Evidence acquisition

2.1. Search strategy

The methods for this systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [9]. MEDLINE (via PubMed), EMBASE, the Cochrane Central Register of Controlled Trials, and guideline statements from professional organizations were queried to identify manuscripts available from January 1, 2000 through January 10, 2018. The initial search strategy included the following different terms: "(<radiotherapy> OR <radiation>) AND <prostatectomy> AND (<salvage> OR <recurrent>)". This yielded 1443 results.

2.2. Inclusion and exclusion criteria

The 1443 abstracts identified were further analyzed according to the PRISMA approach, as depicted in Figure 1. Inclusion criteria included identification based on (1) the additional search term "<PSA>", which yielded 706 results, and (2) the additional search term "(<androgen deprivation> OR <hormonal>)", which yielded 402 results. Further screening of manuscript abstracts to remove erroneous identification and abstracts without a cognate manuscript revealed 302 articles for review. These articles were then screened in detail by a single investigator (A.U.K.) against the following exclusion criteria: (1) did not present primary data; (2) did not specifically analyze the association between pre-SRT PSA and the use of HT and SRT outcomes; (3) included 50 or fewer patients; (4) reported outcomes for a patient population for which a subsequently updated report was available; (5) were not written in English; or (6) did not have full text available. Ultimately, this yielded 16 manuscripts specifically analyzing the importance of the pre-SRT PSA level and 17 manuscripts specifically reporting the impact of concurrent HT with SRT. Outside of two randomized trials evaluating the role of HT, all other reports were retrospective in nature.

2.3. Data extraction

Patient characteristics extracted from each study included a proxy indicator of pre-SRT PSA distribution (generally median PSA), the percentage of patients with pathologic Gleason grade group (GG) 4–5 disease, the percentage of patients with pT3b or pT4 disease, and the percentage of patients with negative margins. Information on the SRT dose and field design was also extracted, along with median HT duration. Outcomes data were obtained for all reported outcomes, including BCR, progression-free survival, distant metastasis (DM)-free survival, PCSM, and overall survival (OS). No statistical tests were performed; findings were interpreted as statistically significant if reported as such, provided the p value was <0.05.

2.4. Assessment of risk bias

The risk of bias for the two randomized controlled trials included in this review was assessed using the Cochrane risk of bias assessment tool for randomized controlled trials [10].

3. Data synthesis

3.1. Timing of SRT

3.1.1. Rationale for early salvage

The European Association of Urology/European Society for Radiotherapy and Oncology/International Society of Geriatric Oncology guidelines emphasize the importance of early SRT, defined as SRT initiated at PSA <0.5 ng/ml [11], while the 2013 American Society for Radiation Oncology/American Urological Association guidelines state that "patients should be informed that the effectiveness of RT for PSA recurrence is greatest when given at lower levels of PSA" [12]. These recommendations are in large part driven by a systematic review of 41 studies that identified an average 2.6% decrement in BCR-free survival for each increment of 0.1 ng/ml in PSA at the time of SRT [13]. However, the optimal pre-SRT PSA remains unclear. Theoretically, PSA is a proxy for disease burden and thus a low pre-SRT PSA suggests a low-volume curable disease burden that is potentially still localized. Alternatively, it is possible that the magnitude of the pre-SRT PSA itself is less