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Prostate Cancer

Impact of Early Salvage Radiation Therapy in Patients with Persistently Elevated or Rising Prostate-specific Antigen After Radical Prostatectomy

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Abstract

Background: Salvage radiation therapy (SRT) is a recommended treatment option for biochemical recurrence after radical prostatectomy (RP). However, its effectiveness may be limited to specific categories of patients.
Objective: We aimed to identify the optimal candidates for early SRT after RP.
Design, setting, and participants: The study included 925 node-negative patients treated with SRT after RP at seven institutions. Patients received SRT for either prostate-specific antigen (PSA) rising, or PSA persistence after RP that was defined as PSA level $\geq$0.1 ng/ml at 1 mo after surgery. All patients received local radiation to the prostate and seminal vesicle bed.
Outcome measurements and statistical analysis: The primary outcome measured was distant metastasis after SRT. Regression tree analysis was used to develop a risk-stratification tool. Multivariable Cox regression analysis and nonparametric curve fitting methods were used to explore the relationship between PSA level at SRT and the probability of metastasis-free survival at 8 yr.
Results and limitations: At a median follow-up of 8.0 yr, 130 patients developed distant metastasis. At multivariable analysis, pre-SRT PSA level was significantly associated with distant metastasis (hazard ratio: 1.01, $p < 0.0001$). However, when patients were stratified into five risk groups using regression tree analysis (area under the curve: 85%), early SRT administration provided better metastasis-free survival in three groups only: (1) low risk: undetectable PSA after RP, Gleason score $\leq$7, and tumour stage $\geq$pT3b, (2) intermediate risk: undetectable PSA after RP with Gleason score $\geq$8, (3) high risk: PSA persistence after RP with Gleason score $\leq$7.
Conclusions: We developed an accurate risk stratification tool to facilitate the individualised recommendation for early SRT based on prostate cancer characteristics. Early

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SRT proved to be beneficial only in selected groups of patients who are more likely to be affected by clinically significant but not yet systemic recurrence at the time of salvage treatment administration.

Patient summary: In patients affected by prostate cancer recurrence after radical prostatectomy, the early administration of salvage radiation therapy is beneficial only for selected subgroups of patients. In this study, these groups of patients were identified.

1. Introduction

The management of biochemical recurrence (BCR) after radical prostatectomy (RP) represents a clinically significant issue for urologists and radiation oncologists, as approximately 30% of patients experience an increase in prostate-specific antigen (PSA) at long-term follow-up after surgical treatment [1].

Salvage radiation therapy (SRT) is one of the recommended treatment options for patients with BCR after RP and is the only one which can offer definitive cure, although its efficacy has been found to be highly dependent on the PSA level at the time of administration [2,3]. Despite the lack of randomised controlled data, several retrospective studies have shown that early SRT (eSRT) administration was associated with improved BCR-free survival [4,5], metastasis-free survival [6], and cancer-specific survival [7]. For these reasons SRT, when indicated, has been recommended to be administered early, specifically at a PSA level $<$0.5 ng/ml [2,3].

Nevertheless, the potential benefit of eSRT must be balanced against the possible detrimental effect on functional outcomes, specifically, urinary continence and erectile function [8]. Indeed, a non-negligible proportion of patients treated with postprostatectomy radiotherapy may experience both early and late high-grade toxicity [9].

Further, whether the effectiveness of eSRT is limited to specific categories of patients remains unknown [10]. The heterogeneous natural history of BCR, which does not invariably translate into clinical progression and cancer related death in all men, has been well established [11–15]. Therefore, a certain proportion of patients with what is destined to be an indolent BCR may be overtreated with eSRT. At the same time, other patients may already be affected by occult systemic disease at the time of PSA rise, thus likely reducing the effectiveness and rationale of instituting salvage local treatment. As such, the identification of the optimal candidate, as well as the most appropriate timing, for SRT is of utmost importance both to maximise cancer control and to avoid overtreatment.

We hypothesised that the impact of eSRT on patient outcomes varies according to the clinical and pathological characteristics of patients, and that earlier administration of SRT is not invariably associated with improved cancer control in all patients. In particular, we defined early treatment as low PSA level, while delayed treatment consisted of higher PSA level. This general assumption was based on the results of previous studies that reported a significant association between PSA level and oncologic outcomes after SRT [4–7,10]. Furthermore, PSA level at recurrence correlates with number of tumour clones and risk of progression [15,16]. Therefore, PSA in the setting of recurrent prostate cancer is an accurate proxy of tumour burden. The assumption that PSA level correlates with treatment timing is further supported by the significant role of PSA kinetics in patients affected by BCR after RP; in this setting, the PSA level increases progressively, but with a different variation over time depending on the tumour burden and the aggressiveness of the disease [4,7]. As such, the aim of this study was to identify the optimal timing for SRT according to the different clinical and pathological characteristics of the patients.

To test this hypothesis, we evaluated a large multi-institutional cohort of patients who were treated with SRT after RP.

2. Material and methods

2.1. Patient population

We identified 991 patients treated with postprostatectomy SRT at seven tertiary referral centres between 1996 and 2009. All patients had histologically confirmed pT2–pT4 pN0 adenocarcinoma of the prostate. No patient received neo-adjuvant or adjuvant hormonal therapy. Radiation therapy was administered for either PSA rising or PSA persistence after RP. Specifically, PSA rising after surgery was defined as undetectable PSA with a subsequent PSA increase within two or more determinations [2], whereas PSA persistence was defined as a serum concentration $\geq$0.1 ng/ml at 1 mo after RP [17].

Patients with missing information for pathologic stage (n = 16), pathologic Gleason score (n = 8), surgical margin status (n = 19), or postoperative PSA level (n = 23) were excluded. These selection criteria yielded 925 evaluable individuals with complete clinical, pathological, and follow-up data.

2.2. Radiotherapy technique

SRT consisted of local radiation to the prostate and seminal vesicle bed. All patients were treated with high-energy photon beams (6–25 mV) at conventional fractionation (1.8–2 Gy/fraction), with a median dose of 68 Gy (interquartile range [IQR]: 66, 70). A three-dimensional conformal approach was used up to 2002. Intensity-modulated radiation therapy was gradually introduced since 2003 in all the involved institutes. The clinical target volume (CTV) was delineated on computed tomography images and included the prostatic bed, the seminal vesicle bed, and periprostatic tissue. Clinical findings, presurgery computed tomography scan, and surgical clips guided the clinicians for the CTV definition. The planned target volume was defined as CTV plus a 0.7–1.0 cm margin to account for organ motion and setup error. The use of hormonal therapy during SRT was not standardised, and its administration and duration was left at the discretion of the treating physician.

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