Original Study

Risk Factors for Disease Progression After Postprostatectomy Salvage Radiation: Long-term Results of a Single-institution Experience

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Abstract

The optimal timing of salvage radiotherapy (SRT) and the important predictors of recurrence after SRT remain controversial. In our retrospective review of 307 men with recurrent prostate cancer undergoing SRT, we found that Gleason score, T stage, surgical margins, and presalvage prostate-specific antigen (PSA) level were associated with progression. This risk increased with incremental increases in presalvage PSA levels and was not influenced by PSA kinetics.

Background: Salvage radiotherapy (SRT) has been successfully used for recurrent prostate cancer after radical prostatectomy; however, the optimal timing of SRT remains controversial. Our objective was to identify the risk factors for disease progression after SRT, with a focus on the pre-SRT prostate-specific antigen (PSA) levels in the modern era of PSA testing. **Patients and Methods:** We performed a retrospective review of 551 consecutive patients who had undergone postradical prostatectomy SRT for recurrent prostate cancer from 2000 to 2013. The exclusion criteria were hormonal therapy before or concurrent with SRT, adjuvant RT, distant metastases, and missing data. Disease progression was defined as a repeat PSA level of $\geq$ 0.2 ng/mL greater than the post-SRT nadir, a continued increase in the PSA level despite SRT, initiation of systemic therapy, local recurrence, nodal failure, and/or distant metastases. Univariate and multivariable Cox regression analysis were performed to identify the predictors of disease progression. Secondarily, PSA kinetics were evaluated in the model and compared using the Akaike information criterion. **Results:** Of the 551 patients, 307 underwent SRT, of whom 134 experienced subsequent disease progression. The median interval to recurrence was 6.03 years (95% confidence interval, 3.74-8.36 years). On multivariable analysis, Gleason score, T stage, positive surgical margins, and pre-SRT PSA level were associated with progression; PSA kinetics did not independently predict for progression. When the pre-SRT PSA level was stratified ($\leq$ 0.30, 0.31-0.50, 0.51-1.00, and $>$ 1 ng/mL), incremental elevations were associated with an increased risk of disease progression. **Conclusion:** Multiple factors predict for progression after SRT. These risk factors could help identify those who would derive the greatest benefit from additional systemic treatment. The findings of the present study also support initiation of early SRT, irrespective of the PSA kinetics.

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Introduction

Disease recurrence develops in up to one third of prostate cancer patients within 10 years after radical prostatectomy (RP). Patients with positive surgical margins, seminal vesicle invasion, extracapsular extension, and/or a high Gleason score have the greatest risk.[1-3] Subsequent salvage radiotherapy (SRT) has been used with curative intent in patients with clinical evidence of isolated local recurrence or a postoperative increase in prostate-specific antigen (PSA) levels. The utility of SRT in this context has been supported by the findings from multiple retrospective studies[4-7] and endorsed by consensus guidelines from the European Association of Urology and American Urologic Association/American Society for Radiation Oncology.[8]

The 2007 nomogram reported by Stephenson et al[5] has been widely used to predict the success of SRT. These investigators found that 48% of patients who received SRT at a PSA level of ≤ 0.50 ng/mL were disease free 6 years after SRT compared with 26% of those treated at higher pre-SRT PSA levels.[5] This finding has been supported by other retrospective studies, which found that SRT improves cause-specific and overall survival compared with observation.[6,7] A 2016 update of the Stephenson nomogram suggests that improved disease outcomes may be achieved with initiation of SRT at PSA values < 0.2 ng/mL,[9] although the optimal PSA level at which to initiate treatment has not been clearly established.

The primary objective of the present study was to examine the risk factors for disease progression after SRT in the modern era of PSA testing in a large cohort of patients with recurrent prostate cancer. Our secondary objective was to examine the value of PSA kinetics, including pre-SRT PSA velocity (PSA-V) and PSA doubling time (PSA-DT), to predict for disease progression.

Patients and Methods

Patient Selection and Treatment

The institutional review board approved the present study. The study included a retrospective cohort of 551 consecutive patients who had undergone RP and postoperative RT to the prostate bed and/or pelvic lymph nodes (either adjuvant or SRT) from 2000 to 2013. The analysis was restricted to patients treated after 2000 to reflect current management challenges in the era of more sensitive PSA testing; before 2000, the PSA detectability limit was 0.5 ng/mL. Patients were excluded from the analysis if they had received adjuvant RT, defined as radiation delivered with an undetectable PSA level and no clinical evidence of disease; received androgen deprivation therapy (ADT) before or concurrent with SRT; had radiographic evidence of distant metastases; were lost to follow-up at time 0; or had missing data for $\geq$ 1 variables. The exclusion criteria and case selection process are outlined in the Supplemental Figure 1 (available in the online version). A total of 307 patients were available for analysis.

Model Variables

Variables were selected for evaluation in the model based on the risk factors identified in the published data. The year of SRT was considered to assess changes over time. The primary variable of interest was the greatest PSA value after RP and before SRT. Earlier published data had suggested that a PSA level of 0.5 ng/mL was an appropriate threshold at which to initiate SRT[5]; however, recent studies have suggested that this threshold should be lower.[9,10] Thus, we categorized the pre-SRT PSA values according to previously reported thresholds into the following categories: ≤ 0.3, 0.3 to 0.5, 0.5 to 1, and > 1 ng/mL. Although more recent studies have suggested that SRT should be initiated at thresholds as low as < 0.1 ng/mL, this range was only detectable in the institutional PSA assays after 2007. To avoid the potential bias of comparing patients treated in an older era versus a more modern era, PSA values ≤ 0.3 ng/mL were not further stratified.

PSA-V and PSA-DT have also been evaluated in several studies as possible predictors of disease progression after SRT.[6,11,12] In the present study, PSA-V was calculated assuming zero-order kinetics and was defined as the increase in PSA per year from the first detectable post-RT PSA level to the greatest pre-SRT PSA value. The PSA-DT was calculated as the ln(2) divided by the change in the natural logarithm of PSA between the first detectable post-RP PSA level and the greatest pre-SRT PSA level.[7] Values were not calculated for patients with only a single increase in PSA after RP and before SRT was initiated or in the case of missing data. If the PSA value at biochemical failure and before SRT were the same, the PSA-DT was not calculated.

The PSA-DT and PSA-V were both evaluated as continuous variables and categorical variables to allow for comparison to previously reported cohorts.[7] All categorical cutpoints were determined a priori. As a categorical variable, the PSA-V was dichotomized as $<$ 0.5 or $>$ 0.5 ng/mL/y and the PSA-DT as $>$ 10 or $<$ 10 months.

Outcome

The primary endpoint of the present study was interval to disease progression after SRT. Disease progression was defined as a serum PSA value of ≥ 0.2 ng/mL greater than the post-SRT nadir followed by another higher value; a continued increase in the serum PSA level despite SRT; initiation of systemic therapy after SRT completion; or the development of local recurrence, nodal failure, or distant metastases. All patients who died of prostate cancer were captured by this definition. The interval to the outcome or censoring was calculated from the completion date of SRT. Patients who did not develop disease progression were censored at loss to follow-up, death from other causes, or the last contact before the end of the study period.

Statistical Analysis

Overview. Descriptive statistics were used to evaluate the baseline patient characteristics. Categorical variables are presented as counts with relative frequencies and continuous variables as mean $\pm$ standard deviation (SD) or median and first and third quartiles, depending on the distribution of the data. All statistical analyses were conducted using SAS, version 9.4. Survival curves were created using GraphPad, version 6.

Progression-free survival curves were created using the Kaplan-Meier estimator and pre-SRT PSA groups using the log-rank test for trend. Using these curves, we report the median time to disease progression and calculated the 95% confidence intervals (CIs) for these values using the log−log transformation method. All P values were from 2-sided statistical tests, and the level of statistical significance was set at .05. All results from the Cox proportional hazard models are presented as hazard ratios (HRs) with 95% CIs.

Cox Proportional Hazards Analysis. Univariate and multivariable Cox proportional hazards regression analyses were performed to