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Estimation of PSA Half-Life Following Salvage Radiation Therapy

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Abstract

Background: We aim to estimate prostate-specific antigen (PSA) half-life after salvage radiation therapy (SRT) in patients with detectable PSA after radical prostatectomy (RP). **Methods:** A total of 272 patients treated with salvage radiotherapy between July 1987 and July 2010 were included in this IRB approved retrospective analysis. The median pre-salvage radiotherapy dose was 0.6 ng/mL (range, 0.2 - 21.9 ng/mL), 47 patients had at least a minimum tumor stage of T3b, 29 had a Gleason score over 7, and median dose was 66.6 Gy (range, 54.0 - 72.4 Gy). **Results:** The estimated PSA half-life in our cohort of patients was 3.0 months (95% CI, 2.9 - 3.2 months; range, 0.5 - 28.5 months). There was no evidence of a statistically significant association between PSA half-life and any baseline clinicopathologic characteristics. The median interval between individual PSA measurements was noted to be 4.6 months (range, 0.1 - 20.4 months). The median interval from the start of radiation therapy to the nadir PSA was 6.3 months (range, 1.3 - 79.1 months). PSA half-life remained approximately 3.0 months when accounting for infrequent and outlier PSA values. **Conclusion:** The PSA half-life after definitive RT has been reported to be approximately 1.6 months. Our analysis found the PSA half-life after SRT to be approximately twice that of patients treated with definitive RT. These results provide useful information to radiation oncologists when counseling patients both before and after SRT regarding expectations about PSA

measurements.

Keywords

Prostate, Salvage, PSA, PSA Kinetics

1. Introduction

Prostate-specific antigen (PSA) measurements are vital for monitoring disease response to treatment [1]. PSA kinetics, such as a shorter PSA doubling time (PSADT) or a rapid PSA velocity, can indicate more aggressive disease and a poorer prognosis. The kinetics of post-treatment PSA has been studied in patients who received either radical prostatectomy or definitive radiotherapy [2]. Zagars *et al.* found a median PSA half-life after definitive radiation therapy to be 1.6 months. After radical prostatectomy, the median PSA half-life is 3 days [3]. To our knowledge, no study has evaluated the PSA half-life after salvage radiotherapy (SRT). In this study, we sought to estimate the PSA half-life after SRT.

2. Methods

2.1. Study Subjects and Data Collection

All patients treated between July 1987-July 2010 with SRT for detectable PSA after RP at Mayo Clinic Florida (MCF) or Mayo Clinic Rochester (MCR) were considered for inclusion in this study, after approval by the Institutional Review Board of the Mayo Clinic. Patients were excluded if they had hormone therapy prior to SRT (N = 65) or thereafter (N = 12), if they did not have any post-SRT PSA measurements (N = 20), or if post-SRT PSA levels did not drop to less than or equal to 50% of the pre-SRT levels, which precluded PSA half-life estimation (N = 85). Given the latter exclusion criteria, it is worth noting that our study essentially estimated PSA half-life in patients for whom SRT is initially successful to some degree. Additionally, all PSA measurements after reaching their lowest level for a given patient were excluded, and we did not consider any PSA measurements obtained after the start of post-SRT hormone therapy. Patients did not receive concomitant hormonal therapy during SRT. After applying these exclusions, a total of 272 patients (192 MCF, 80 MCR) were included in this retrospective study. In addition to pre-SRT and post-SRT PSA levels, the following information was collected from patients' medical records: age at start of SRT, pre-RP PSA, pathological tumor stage, Gleason score, surgical margin, and SRT dose.

2.2. Statistical Analysis

To estimate PSA half-life after SRT, the following linear regression model was fit to each patient separately, where $\log(PSA_t)$ represents the natural logarithm of PSA at time t, t is the number of months following the start of SRT, and pre-SRT

PSA is the given patients PSA level at $t = 0$.

$$\log\left(PSA_t\right) = \beta_0 - \beta_1 t$$

PSA half-life was estimated for each patient individually by using $\log(2)/\beta_1$. Mean and median half-life was estimated along with 95% confidence intervals. PSA half-life was also summarized using the standard deviation (SD), interquartile range (IQR), and range. In addition to estimating PSA half-life in the overall sample, we also conducted a sensitivity analysis excluding patients who had any interval longer than 365 days between PSA measurements, since PSA half-life is likely less precise for patients with infrequent PSA measurements. Associations between baseline patient characteristics and PSA half-life were evaluated using either Spearman's test of correlation or a Wilcoxon rank sum test. P-values of 0.05 or less were considered statistically significant. All analyses were performed using SAS (Version 9.3, SAS Institute Inc., Cary, NC) and R Statistical Software (version 2.11.0; R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Characteristics of the 272 study patients and the post-SRT PSA measurement information are summarized in Table 1. The median age was 67 years (Range: 45 - 85 years), median pre-SRT PSA level was 0.6 ng/ml (Range: 0.2 - 21.9 ng/ml), 47 (17%) patients had a pathological tumor stage of T3b or higher, 29 (12%) had a Gleason score higher than 7, and the median SRT dose was 66.6 Gy (Range: 54.0 - 72.4 Gy).

A total of 507 post-SRT PSA measurements from the 272 patients were utilized in the estimation of PSA half-life. The median length of time between PSA measurements was 4.6 months (Range: 0.1 - 20.4 months). The median interval from the start of SRT to the first post-SRT PSA visit was 4.7 months (Range: 0.7 - 13.8 months), and the median length of time from the start of SRT to the lowest PSA measurement was 6.3 months (Range: 1.3 - 79.1 months).

As shown in Table 2, estimated PSA half-life was a median of 3.0 months (95% CI: 2.9 - 3.2 months), with an IQR of 2.1 to 4.8 months, and a range of 0.5 to 28.5 months. The distribution of PSA half-life is displayed in Figure 1. When excluding the 11 patients with any interval between PSA measurements longer than 365 days, these estimates did not noticeably change (Table 2).

In the overall cohort of 272 patients, we also examined associations between baseline patient characteristics and PSA half-life. The strongest associations that were observed, although not statistically significant, were with pre-SRT PSA, where a higher value was associated with a shorter PSA half-life (Spearman's r: −0.12, P = 0.054) and surgical margin, where patients with positive margins had a slightly shorter PSA half-life than patients with negative margins (Median: 2.9 vs. 3.1, P = 0.088). There was not an association between PSA half-life and age (P = 0.87), pre-RP PSA (P = 0.72), pathological tumor stage (P = 0.64), Gleason score (P = 0.20), or SRT dose (P = 0.81).

Table 1. Patient characteristics and PSA measurement information.

Variable	Summary (N = 272)
Age at start of SRT (years)	67 (45 - 85)
Pre-RP PSA (ng/ml)	8.4 (0.0 - 219.0)
Pre-SRT (PSA (ng/ml)	0.6 (0.2 - 21.9)
Pathological tumor stage	
T2	136 (50%)
T3a	88 (32%)
T3b	46 (17%)
T4	1 (<1%)
Gleason score	
1 - 6	101 (42%)
7	108 (45%)
8 - 10	29 (12%)
Surgical margin	
Positive	145 (54%)
Negative	123 (46%)
SRT dose (Gy)	66.6 (54.0 - 72.4)
Visit interval (months) start of SRT to 1st visit (N = 272)	4.7 (0.7 - 13.8)
1st to 2nd visit (N = 118 patients with 2 visits)	3.7 (0.1 - 20.4)
2nd to 3rd visit (N = 55 patients with 3 visits)	4.4 (1.0 - 13.3)
3rd to 4th visit (N = 33 patients with 4 visits)	4.6 (1.0 - 16.3)
4rd to 5th visit (N = 14 patients with 5 visits)	4.6 (1.1 - 12.6)
5th to 6th visit (N = 9 patients with 6 visits)	7.2 (1.1 - 11.0)
Start of SRT to lowest PSA measurement (months)	6.3 (1.3 - 79.1)

The sample median, minimum and maximum is given for numerical variables. Information was unavailable for the following variables: pathological tumor stage (N = 1), Gleason score (N = 34), and surgical margin (N = 4). GY: gray; PSA: prostate serum antigen; SRT: salvage radiation therapy; RP: radical prostatectomy.

Table 2. Estimates of PSA half-life.

Patient Group	Estimated PSA Half-Life (months)
All 272 patients	
Mean (95% CI)	4.3 (4.0 - 4.7)
Median (95% CI)	3.0 (2.9 - 3.2)
Standard deviation	4.2
Interquartile range	2.1 - 4.8
Range	0.5 - 28.5
Excluding patients with any interval between PSA measurements longer than 365 days (N = 261)	
Mean (95% CI)	4.0 (3.6 - 4.3)
Median (95% CI)	2.9 (2.8 - 3.1)
Standard deviation	3.6
Interquartile range	2.1 - 4.5
Range	0.5 - 28.5

CI: confidence interval, PSA: prostate-specific antigen.

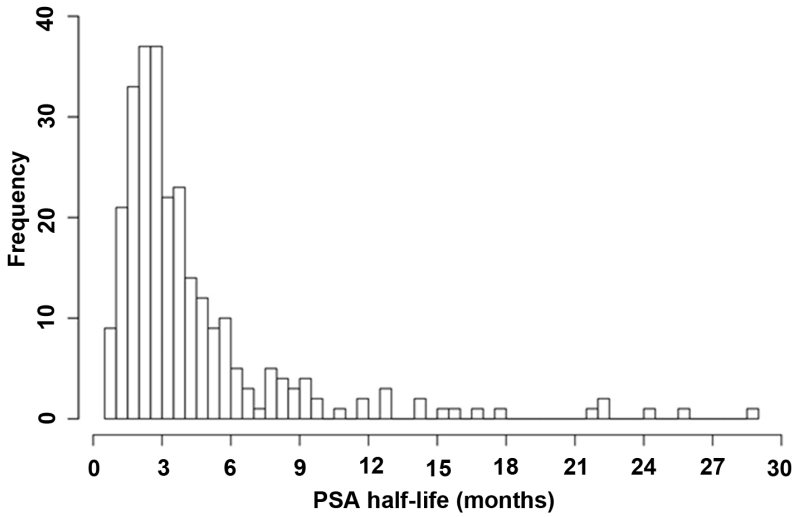

Figure 1. PSA half-life distribution by number of patients (n = 272). Median PSA half-life was 3.0 months and this did not change significantly once removing PSA half-lives over 365 days.

4. Discussion

PSA is a well-established and reliable serum biomarker for monitoring disease status in the post-radical prostatectomy setting [4] [5] [6]. After either definitive or SRT, there is a delayed response in PSA levels, because prostate cancer cell death occurs gradually over a variable and sometimes prolonged timeframe [7] [8] [9]. Similar declines in growth hormone and prolactin levels have been seen after pituitary irradiation [10] [11]. From our observations, the reduction of serum PSA levels after SRT appears to follow first order kinetics, as noted for definitive radiotherapy by Zagars and others [2] [12] [13] [14] [15]. PSA half-life determinations following definitive radiotherapy include the PSA response of both normal prostate tissue and prostate cancer, but it represents prostate cancer kinetics only with post-prostatectomy SRT. This study is the first study to our knowledge to evaluate PSA kinetics without such confounding.

The median estimated PSA half-life for patients receiving SRT in our study patients was 3.0 months. In a study of 841 men who underwent definitive primary radiotherapy, Zagars *et al.* found that median PSA half-life was 1.6 months [2]. A smaller study by Ritter et al of 63 patients who underwent definitive radiotherapy observed a median PSA half-life of 2.6 months [5]. Related to this, the degree of variability in PSA half-life appears to be greater after RT compared to definitive radiotherapy. Specifically, the maximum PSA half-life was 28.5 months in our study, which is far higher than the 9.2 months reported by Zagars *et al.* [2] and the approximately 7 months reported by Ritter *et al.* [5] Furthermore, the SD of PSA half-life was greater in our study (4.2 months) compared to that of Ritter *et al.* 5 (1.3 months), and there was a generally greater degree of variability in PSA half-life evident in the frequency histogram displayed in our study (**Figure 1**) compared to that of the other two studies [2] [5]. It is unclear why there may be a longer half-life in the SRT setting, but it may be related to relative hypoxia in

the tumor microenvironment (in a postoperative state), intrinsic tumor heterogeneity or prognostic factor differences between these study populations.

Although not quite statistically significant, we observed a correlation between increased pre-SRT PSA and a shorter PSA half-life; however, the magnitude of this correlation was fairly small and therefore of questionable clinical significance. This finding is in line with that of Zagars *et al.* [2], who observed a statistically significant association with a shorter half-life in patients with a higher pre-treatment PSA, but noted that the degree of correlation was weak. The study by Ritter *et al.* [5] did not observed a significant association between pre-treatment PSA level and PSA half-life, and neither our study nor those by Zagars [2] or Ritter [5] observed a significant association between PSA half-life and either Gleason score or pathological tumor stage. We should note that lack of statistical associations between baseline characteristics and PSA half-life does not exclude its possibility. The exclusions we applied to identify our study cohort and its limited size may not be sufficient for this purpose.

5. Conclusion

PSA measurements continue to be a useful tool in measuring treatment response. Our study defines the kinetics of PSA half-life with SRT and suggests that PSA values decrease slightly more slowly compared to after definitive radiotherapy. These results provide useful information to radiation oncologists when counseling patients both before and after SRT regarding expectations about PSA measurements.

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List of Abbreviations

PSA—Prostate Specific Antigen
SRT—Salvage Radiotherapy
SD—Standard Deviation
IQR—Interquartile Range
MCR—Mayo Clinic Rochester
MCF—Mayo Clinic Florida