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Scientific Article

# Interim Prostate-Specific Antigen: Predicting for Biochemical Failure During Salvage Radiation Therapy After Prostatectomy

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**Abstract**

**Purpose:** A subset of patients treated with postprostatectomy radiation therapy for biochemical recurrence after surgery fail to respond because of microscopic disease beyond the irradiated prostate bed. This work aims to determine whether a rising interim prostate-specific antigen (PSA) during radiation therapy can predict the likelihood of subsequent biochemical recurrence.

**Methods and Materials:** Between 2010 and 2016, 185 patients had salvage radiation therapy to a dose of 68 Gy without androgen deprivation therapy for a rising PSA level after radical prostatectomy. Patients had their PSA recorded on the first day of radiation therapy and again after completing the 25th fraction (of 34 total fractions). Biochemical failure after radiation therapy was defined as a PSA value $\geq$0.2 ng/mL within 2 years after radiation therapy. Both univariate and multivariate Cox regression models were used for statistical analysis. Factors with a $P$ value of $<$.2 in univariate analysis were then used in a multivariate analysis.

**Results:** The 2-year freedom from biochemical failure was 60% (95% confidence interval, 53%-67%). When assessing the interim PSA, 143 patients (77%) had a drop in interim PSA; of these patients, 71% had 2-year biochemical control. Forty-two patients (23%) had a stable or rising interim PSA, and only 24% of these patients had 2-year biochemical control. On multivariate analysis, a drop in PSA during radiation therapy ($P < .0001$) and a positive surgical margin ($P < .0001$) were significant factors for freedom from subsequent biochemical failure, and seminal vesicle invasion was associated with biochemical failure at 2 years ($P = .019$). All patients with a rising interim PSA, negative surgical margin, and seminal vesicle invasion ultimately had biochemical failure at 2 years.

**Conclusions:** A PSA rise during salvage radiation therapy is prognostic of biochemical failure at 2 years. Factors such as seminal vesicle invasion and a negative surgical margin also predict for poor responders to salvage radiation therapy.



## Introduction

Approximately 30% of men with localized prostate cancer will develop detectable prostate-specific antigen (PSA) levels after a radical prostatectomy, and two-thirds of these men will develop metastatic prostate cancer if left

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untreated.[1,2] Several randomized clinical trials (eg, SWOG 8794, German ARO 9602, and EORTC 22911)[3-5] have demonstrated that adjuvant radiation therapy within 6 months of surgery improves biochemical failure—free survival by 20% to 25%. Whether to give adjuvant radiation therapy versus observation with salvage treatment at the time of biochemical relapse remains an area of controversy and is being investigated by several randomized trials.[6,7]

The recently completed RAVES trial showed similar freedom from biochemical failure rates between adjuvant radiation therapy and observation with salvage treatment, but the protocol defined level set for noninferiority was not achieved. Observation with salvage treatment did spare approximately half of men from pelvic radiation therapy and is associated with significantly lower levels of genitourinary toxicity.[8]

Salvage radiation therapy after a rise in PSA after a radical prostatectomy offers a second chance at a cure, with salvage radiation therapy resulting in long-term biochemical control rates of approximately 50%.[9-11] Current American Urological Association and European Association of Urology guidelines support prostate bed radiation therapy as a standard treatment for patients with a rising PSA after a radical prostatectomy for prostate cancer.[12,13]

There are known prognostic factors and nomograms that predict for failure after salvage radiation therapy.[14] Patients who biochemically recur after salvage radiation therapy are likely to have undetected microscopic disease beyond the prostate bed. However, even patients with poor prognostic factors have a chance of biochemical control, making it difficult to determine who should not be offered salvage radiation therapy.

Restaging with a Gallium prostate specific membrane antigen (PSMA) positron emission tomography (PET) scan at the time of biochemical relapse improves the chances of detecting macroscopic tumor compared with conventional imaging.[15] However, despite the increased sensitivity of PSMA PET imaging, at ultralow PSA levels, macroscopic disease often cannot be detected. Schmidt-Hegemann et al have shown that with PSA values <0.2 ng/mL, detection rates with PSMA PET are only 33.3%.[16] Most patients are considered for salvage postprostatectomy radiation therapy with a PSA level <0.2 ng/mL. The efficacy of salvage radiation therapy in an era of ultrasensitive PSA readings has been demonstrated when salvage radiation therapy is delivered at low PSA values, with improved 5-year biochemical relapse—free survival when this occurs.[17]

Therefore, even with PSMA PET restaging, in most cases clinicians will rely on prognostic factors to predict whether patients will have prostate bed recurrences or recurrences outside of the pelvis. More sensitive techniques are needed to determine whether a patient has pelvis-confined recurrent disease, which is suitable for salvage radiation therapy, or metastatic disease for which local treatment would be futile. A falling PSA during salvage postprostatectomy radiation therapy may be the earliest indication that a patient does have at least a component of residual disease in the prostate bed. Conversely, a rising PSA during salvage radiation therapy may suggest that a patient has disease beyond the radiation therapy field and therefore is destined to fail salvage prostate bed radiation therapy.

## Methods and Materials

### Cohort of patients

This is a single-center study of all postprostatectomy patients with a detectable postoperative PSA treated with salvage radiation therapy without androgen deprivation therapy (ADT) from 2010 to 2016. Patients had their PSA measured on the first day of radiation therapy and again after completing the 25th fraction (of 34 total fractions). Patients were included if they had histologic confirmation of prostate adenocarcinoma, no evidence of metastasis, and PSA measurements out to 2 years from treatment. Patients were excluded if they had ADT therapy, no detectable PSA postoperatively, had adjuvant radiation therapy, were node positive, or had whole-pelvis radiation therapy. The electronic medical records of all patients on MOSAIQ (Elekta Medical Systems, Sunnyvale, CA) who underwent salvage radiation therapy between the years of 2010 and 2016 were reviewed retrospectively. Patient data were deidentified and measures were collated, including the patient age; PSA before, during, and up to 2 years after treatment; and tumor factors (eg, Gleason score and T stage).

### Radiation therapy treatment

Patients received 68 Gy in 34 fractions (2 Gy per fraction, 5 fractions per week) using a 3-dimensional conformal external beam radiation therapy technique (2010-2014) or an intensity modulated radiation therapy/volumetric modulated arc therapy external beam radiation therapy technique (2014-2016). Daily cone beam computed tomography images with soft tissue matching was used. These patients did not receive ADT and did not have pelvic lymph nodes treated with radiation therapy.

### Follow-up and definition of biochemical failure after salvage radiation therapy

The first PSA was drawn on the first day of radiation therapy and on the day of the 25th fraction of radiation therapy. Patients then had subsequent PSA blood tests at 3, 12, and 24 months after radiation therapy treatment.

Biochemical failure was defined as having a PSA value ≥0.2 ng/mL after salvage radiation therapy.

## Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, version 25.0, IBM Corp, Armonk, NY). When assessing for biochemical failure, all variables other than age and the PSA at the time of radiation therapy were dichotomized, and univariate and multivariate Cox regression models were used. Variables used in the univariate analysis include age, PSA at the time of radiation therapy, PSA doubling time less than 3 months before salvage radiation therapy (for a subset of 160 patients), a drop in PSA between fraction 1 and fraction 25, a detectable postoperative PSA, a Gleason score >7, surgical margin positivity, seminal vesicle invasion, extracapsular extension, and the presence of a pelvic lymph node dissection. Variables that affected biochemical failure—free survival with a $P$ value of <.2 were used in a multivariate Cox regression calculation. Significance was determined when the $P$ value was <.05. Kaplan-Meier survival curves were also created in SPSS.

## Results

There were 185 patients in total and patient characteristics are shown in Table 1. The median age was 66 years. Of the 185 patients, 34.1% had pT2 disease and 65.9% had pT3 disease. Most patients (78.9%) had a Gleason score of 7, 17.8% had a Gleason score >7, and only 3.2% had a Gleason score ≤6. A pelvic lymph node dissection was performed in 75.7% of patients (all patients were lymph node negative), and a positive surgical margin was found in 60.5% of the patients.

The overall 2-year biochemical relapse—free survival in this cohort of 185 patients was 60% (95% confidence interval, 53%-67%). In addition, 143 patients (77%) had a drop in interim PSA, and of these patients 71% had 2-year biochemical control. Forty-two patients (23%) had a stable or rising interim PSA, and only 24% (10 patients) had 2-year biochemical control. Figure 1 demonstrates increased biochemical failure free survival in patients who have a drop in PSA during salvage radiation therapy.

## PSA before and during radiation therapy for biochemical failure

On univariate analysis, a falling PSA between the first and 25th fractions proved to be an independent factor predicting biochemical failure at 2 years, with a hazard ratio (HR) of 0.385 (0.243-0.611; $P$ < .001). A persistently detectable postoperative PSA or the PSA level before radiation therapy did not have a statistical association with biochemical failure at 2 years. The PSA doubling time before radiation therapy was also assessed for 160 of the 185 patients, but this was not found to have a statistically significant effect on biochemical failure—free survival.

## Prognostic pathologic factors for biochemical failure

On univariate analysis, several tumor-related factors were found to affect biochemical failure with statistical significance. These factors included a Gleason score >7 ($P$ = .041) with an HR of 1.706 (1.021-2.850), a positive surgical margin ($P$ < .0001) with an HR of 0.397 (0.248-0.635), and seminal vesicle invasion ($P$ = .006) with an HR of 1.987 (1.221-3.232). The presence of extracapsular extension did not affect the probability of biochemical failure—free survival at 2 years.

## Other factors for biochemical failure

It was found that a patient's age and whether a patient had pelvic lymph node dissection did not have a statistically significant effect on biochemical failure at 2 years.

**Table 1** Patient and tumor details

| Characteristic | No. (%) |
|---|---|
| Age (y) | |
| <60 | 49 (26.5) |
| 61-70 | 104 (56.2) |
| >71 | 32 (17.3) |
| Gleason score | |
| <6 | 6 (3.2) |
| 7 | 146 (78.9) |
| 8-10 | 33 (17.8) |
| Pelvic lymph node dissection | |
| Yes | 140 (75.7) |
| No | 45 (24.3) |
| Pathologic T stage | |
| T2 | 63 (34.1) |
| T3a | 85 (45.9) |
| T3b | 37 (20.0) |
| Surgical margins | |
| Positive | 112 (60.5) |
| Negative | 73 (39.5) |
| Pre—radiation therapy PSA (ng/mL) | |
| 0.01-0.1 | 92 (49.7) |
| >0.1-0.2 | 52 (28.1) |
| >0.2 | 41 (22.2) |

*Abbreviation*: PSA = prostate-specific antigen.

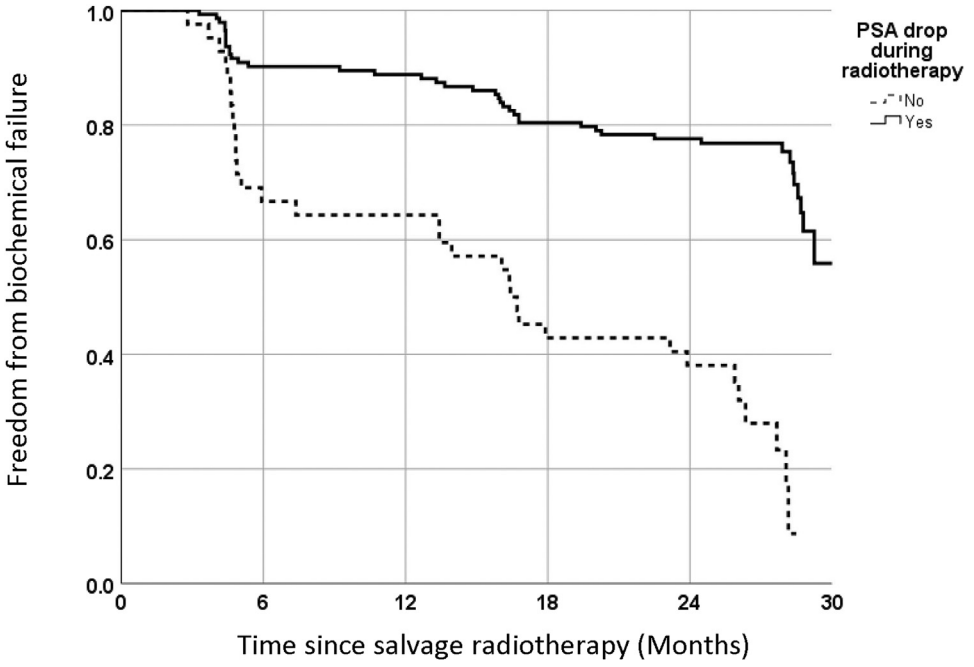


**Figure 1** Biochemical failure—free survival for patients with a drop in prostate-specific antigen (PSA) during salvage radiation therapy.

## Overall prognostic factors for biochemical failure from multivariate analysis

A multivariate analysis for biochemical failure was performed using exact time points including a drop in PSA during radiation therapy, a Gleason score >7, positive surgical margins, and seminal vesicle invasion. It was found that they were all statistically significant contributors to biochemical failure except a Gleason score >7 ($P = .194$).

The multivariate analyses for prognostic factors affecting biochemical failure at 2 years are shown in Table 2. The drop in PSA during radiation therapy ($P < .0001$) had an HR of 0.288 (0.174-0.476). The presence of a positive surgical margin ($P < .0001$) had an HR of 0.343 (0.211-0.559). The presence of seminal vesicle invasion ($P = .019$) had an HR of 1.837 (1.104-3.056). Even though there were only 5 patients, all patients with a rising PSA, negative surgical margins, and seminal vesicle invasion had biochemical failure within 2 years.

## Discussion

Multiple pathologic and biochemical prognostic factors that predict the outcome of salvage radiation therapy are known.[14,17] However, even in the presence of multiple poor prognostic factors, some patients will be successfully salvaged with radiation therapy to the prostate bed. Although PSMA PET scanning detects metastatic disease earlier than conventional staging, it still lacks sensitivity in men with ultralow PSA values (<0.2 ng/mL). Many men are referred for consideration of salvage radiation therapy with PSA levels <0.2 ng/mL, and there is mounting evidence that the lower the PSA when salvage radiation therapy commences, the better the chances of successful salvage. Hence, better tools to identify patients who will not be cured by salvage radiation therapy are needed.

De Crevoisier et al have previously shown that when treating prostate cancer in an intact prostate using radiation therapy with or without ADT, a PSA level drop 6

**Table 2** Prognostic factors for biochemical failure at 2 years on multivariate analysis using PSA values at exact time points

| | Interim PSA | | Surgical margins | | Seminal vesicle invasion | | Gleason score | |
|---|---|---|---|---|---|---|---|---|
| | Same or rise | Fall | Negative | Positive | Yes | No | >7 | ≤7 |
| HR (95% CI) | 3.472 (2.101-5.747) | 1* | 2.915 (1.789-4.739) | 1* | 1.837 (1.104-3.056) | 1* | 1.427 (0.834-2.440) | 1* |
| *P* value | <.0001 | | <.0001 | | .019 | | .194 | |

*Abbreviations*: CI = confidence interval; HR = hazard ratio; PSA = prostate-specific antigen.
* Reference value.

weeks after radiation therapy has commenced has positive implications for prostate cancer—specific survival.[18] Patients with an intact prostate are expected to have potential fluctuations in PSA levels during radiation therapy treatment owing to normal glandular acinar tissues of the prostate responding to radiation therapy and causing a release of PSA. It is thought that in the post—radical prostatectomy setting that there would not be enough normal glandular acinar tissue remaining for this fluctuation in PSA to occur. Hence, an increase in PSA during radiation therapy in the salvage radiation therapy context would presumably be due to a source of PSA secretion into the bloodstream outside of the pelvis.

A smaller series with 41 patients in the post prostatectomy setting performed by Do et al has also shown that a drop in PSA during a course of salvage radiation therapy is associated with better biochemical disease-free survival.[19] Wiegel et al looked at PSA measurements during salvage radiation therapy after a radical prostatectomy for 41 patients (at 30 Gy, 50 Gy, and 60 Gy) and found that nearly all patients with a continued PSA rise between 50 Gy and 60 Gy did not stand to profit from radiation therapy.[20] The present study is investigating the use of an interim PSA in a larger patient cohort to provide an early indication of the efficacy of salvage radiation therapy and whether the prognostic value of existing prognostic factors can be improved.

This study demonstrates that a fall in the PSA during salvage radiation therapy is a statistically significant positive independent prognostic factor for biochemical failure—free survival at 2 years. The corollary is that a patient who has a rising PSA during salvage radiation therapy is likely to ultimately fail treatment. Other identified tumor-related variables that affect biochemical failure—free survival include a positive surgical margin, which was a significant factor for freedom from biochemical failure; seminal vesicle invasion and a Gleason score $>7$ were associated with biochemical failure at 2 years on univariate analysis.

These univariate results agree with a previous study that demonstrated major factors that contribute to biochemical failure include a Gleason score $>7$, negative surgical margins, and seminal vesicle invasion.[9] Blanchard et al found that the absence of PSA level decline during salvage radiation therapy was prognostic of biochemical and clinical failure, which also supports this work's findings.[21] On multivariate analysis, a Gleason score $>7$ was no longer a statistically significant contributor to biochemical failure at 2 years, while a drop in PSA during radiation therapy, a positive surgical margin, and a lack of seminal vesicle invasion all remained positive predictors for freedom from biochemical failure.

A significant amount of evidence supports the use of salvage radiation therapy after radical prostatectomy.[8,10,11] However, salvage radiation therapy treatment is associated with a risk of acute and late bladder and bowel toxicities.[22] Identifying patients who are likely to have biochemical failure after prostate bed radiation therapy may allow these patients to avoid futile treatment.

A rising PSA during salvage radiation therapy is highly prognostic of ultimate treatment failure and suggests occult metastases beyond the radiation therapy field. These data demonstrate that a rising interim PSA in combination with negative surgical margins predicts a remarkably high chance of disease beyond the prostate bed. Patients with a stable or rising PSA should be monitored more closely after completion of treatment, given their high propensity for biochemical failure.

There are limitations to this study. This study was based on a retrospective analysis of nonrandomized data from one institution. No analysis of overall survival was performed because minimal events occurred (no deaths occurred in these patients) in the follow-up period of 2 years. A limitation of this study is that were a low number of patients with Gleason score 8 to 10, and the Gleason score was dichotomized limiting its interpretability, particularly on multivariant analysis. The strength of this study is that selection bias is noncontributory because the data were derived from consecutive patients referred for consideration of salvage radiation therapy between 2010 and 2016. Furthermore, a large amount of patient data was used in this study. This study has shown that PSA during radiation therapy can be used as an indicator of the effectiveness of salvage radiation therapy and a predictor for biochemical failure at 2 years.

## Conclusions

This study has shown that a drop in PSA during salvage radiation therapy is a strong independent prognostic factor predicting for freedom from biochemical failure at 2 years. Other tumor-related factors such as seminal vesicle invasion and a negative surgical margin also predict for poor responders to salvage radiation therapy.

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