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Original article

Predicting PSA failure following salvage radiotherapy for a rising PSA post-prostatectomy: From the CaPSURE™ database☆

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Abstract

Background: The role of radiotherapy (RT) for rising PSA after radical prostatectomy (RP) is debatable. We analyzed a large database of men to evaluate for predictors of prostate-specific antigen (PSA) failure after salvage RT.

Methods: Data from the Cancer of the Prostate Strategic Urologic Research Endeavor database (CaPSURE™) identified 4,563 men with RP between 1989 and 2004; 194 underwent salvage RT ≥6 months after RP. PSA failure following RT was defined as a PSA >0.2 ng/ml. The association between clinical and pathologic characteristics and PSA failure was examined using a χ-square metric. A multivariable analysis of predictors for time to PSA failure was performed using a Cox proportional hazard regression model.

Results: After a median follow-up of 66 months, 121 (62%) men experienced PSA failure at a median 20 months. Significant associations for PSA failure were found for the clinical T category ($P < .01$), race/ethnicity ($P = 0.04$), pT3 disease ($P < 0.01$), seminal vesicle invasion ($P < 0.01$), and pre-RT PSA level ($P < 0.01$). The pre-RT PSA level ($P = 0.07$) was the only factor to approach significance as an independent predictor of PSA failure on multivariable analysis. Pre-RT PSA doubling time was calculated for 131 men but did not predict for PSA failure on univariate ($P = 0.38$) or multivariate analyses ($P = 0.13$) for ≤12 vs. >12 months.

Conclusions: Salvage RT provided the greatest benefit in PSA control in men with the lowest pre-RT PSA levels. Post-RP PSA doubling time >12 months trended toward predicting for PSA failure but was not significant likely owing to limited sample size. Together, these findings would suggest that salvage RT is optimal at low pre-RT PSA and long doubling times with favorable pathologic features.

Keywords: Prostate cancer; Prostatectomy; Radiation therapy; Salvage

1. Introduction

The serum determination of prostate-specific antigen (PSA) has led to earlier diagnosis of asymptomatic prostate cancer that is generally organ-confined [1]. Radical prostatectomy (RP) provides excellent results in men with organ-confined disease [2]. Nevertheless, reports indicate that 15% to 53% of men will develop a detectable PSA following RP [3–7]. Although controversial, management options for a recurrent or rising PSA include observation, androgen deprivation therapy (ADT), salvage external beam radiotherapy (RT) to the prostatic fossa, or combinations of these therapies.

Retrospective reports reveal that 25% to 80% of men undergoing salvage RT will in fact experience durable PSA response, suggesting a potential for cure using this modality [8–16]. Single and multi-institutional reports indicate that Gleason score, surgical margin status, seminal vesicle involvement, extra-capsular extension, the time from surgery to detectable PSA, PSA doubling time prior to salvage, and pre-RT PSA level are variables that predict for PSA re-

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sponse to salvage RT [8–17]. Men with more favorable disease characteristics, including Gleason grade 6 or less disease, positive surgical margins and a PSA < 1.0 ng/ml prior to RT, have been reported to have a ≥70% probability of durable PSA response after salvage RT [11,12,14,16]. Series have also indicated that salvage RT controls locally recurrent, palpable disease, although durable PSA response in this setting is modest at best [8,18–21].

Recently, three large randomized studies of immediate postoperative (adjuvant) RT compared with observation following RP in men with pT3 disease reported a significant improvement in PSA relapse-free survival of >20% favoring those receiving RT [22–24]. Unfortunately, there is currently no Phase III data addressing the use of RT in the salvage setting.

Two reports have each presented a nomogram or predictive model that can be applied in the setting of a rising PSA after RP to determine the potential benefit of salvage RT [14,16]. In an effort to assist the physician with the clinical decision regarding the use of salvage RT, we retrospectively analyzed a prospective, longitudinal observational database to identify predictors of durable PSA response following salvage RT.

2. Methods

Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE™) is a longitudinal observational study of prostate cancer patients within the United States. The database was created in 1995 and has enrolled more than 12,000 patients, making it one of the largest nonrandomized longitudinal databases of prostate cancer in a conventional, community-based setting (www.capsure.net). Clinical data is entered into CaPSURE™ from 65 clinical practices by participating physicians on men who have consented to be in the study.

Of 4,563 men who underwent prostatectomy from 1989 to 2004 in CaPSURE™, 237 received RT as salvage therapy. Within CaPSURE™, salvage RT is defined as RT delivered at a minimum 6 months postoperatively for a man with a detectable PSA. The analyzed set for salvage RT consisted of 194 (4%) men for whom complete information was available. All eligible men did not receive ADT prior to or as a component of salvage RT.

Information gathered from the database and used in the ensuing analysis included sociodemographic, clinical, and pathologic data. Information regarding RT technique, dose, and toxicity was not consistently nor comprehensively tracked in the database so this information was not included in the analysis.

Time to any failure or death up was calculated from the first day of treatment. Follow-up with serial serum PSA levels occurred at variable time intervals and frequencies according to the independent physicians' preferences. PSA doubling time (PSA DT) was calculated in 131 men using all PSA measurements following RP but prior to salvage RT. The calculation of PSA DT assumed first order kinetics, dividing the natural log of 2 by the slope of the log PSAs vs. time of PSA measurements for each man.

PSA failure after salvage was defined as a PSA >0.2 ng/ml (confirmed by a second PSA examination) or initiation of additional therapy. Differences between patients who did or did not experience failure were assessed by χ-square analysis for categorical variables and analysis of variance (ANOVA) for continuous variables. Cox regression multivariable analysis [25] with backward selection for the PSA failure endpoint was performed, adjusting for those factors that reached statistical significance on the exploratory analyses. Significance was declared for a $P < 0.05$.

3. Results

Complete information was available for 194 men who received salvage RT without ADT. Salvage RT was initiated a median of 24 months following RP (lower and upper quartile range 14 to 42 months). Within CaPSURE™, of the 4,563 men who underwent RP but did not receive salvage RT, 297 (6.5%) initiated hormonal therapy at a median 23 months postoperatively. Two more men received cryosurgery as salvage following RP. Pre- and postoperative characteristics of the analyzed cohort are presented in Table 1.

The median follow-up from salvage RT was 66 months (SD: 40 months). The mean pre-RT PSA was 1.4 ng/ml (range: 0.3–8.9 ng/ml). At a median 20 months (SD: 19 months) following salvage RT, 121 (62%) men met criteria for PSA failure.

Significant differences in PSA failure based on clinical T category ($P < 0.01$), race/ethnicity ($P = 0.04$), seminal vesicle invasion ($P < 0.01$), pT3 disease ($P < 0.01$), and pre-RT PSA level ($P < 0.01$) were observed. Among those for whom PSA DT was calculated ($n = 131$), 15 of 46 men (33%) failed whose PSA DT was ≤12 months. For PSA DT >12 months, 20 of 85 (24%) men failed ($P = 0.38$).

The multivariable analysis for time to PSA failure included the following pre- and post-treatment factors: race/ethnicity, clinical T category, surgical Gleason score, PSA at diagnosis, time from RP to salvage, pre-RT PSA, pre-RT PSA DT, and pathologic T3 disease. Pre-RT PSA DT independently predicted for PSA failure (Table 2). The pre-RT PSA level ($P = 0.07$) was the only factor to approach significance as an independent predictor of PSA failure. PSA DT trended towards significantly predicting PSA failure whether analyzed as ≤12 vs. >12 months (Table 2) or when analyzed as ≤3 months ($n = 4$), 3 to 12 months ($n = 42$), or >12 months ($n = 85$) (HR 1.4 CI 0.3–6.1 for 3 to12 months; HR 0.8 CI 0.2–3.6 for >12 months; compared with ≤ 3 months, $P = 0.16$ for trend). PSA failure-free survival adjusted for the pre-RT PSA level is depicted in Fig. 1. An analysis of pre-RT PSA and PSA DT showed no statistically significant association ($P = 0.7$).

Table 1
Clinical and pathological characteristics of men receiving salvage RT (n = 194)

Characteristic	No. (%)
Age at diagnosis (yrs)	
<55	34 (18)
55–64	80 (41)
65–74	79 (41)
≥75	1 (0)
Race/Ethnicity	
Black	19 (10)
White	145 (75)
Other	30 (15)
PSA at diagnosis (ng/ml)	
<4	16 (8)
4.1–10	90 (46)
10.1–20	52 (27)
>20	36 (19)
Clinical T category	
T1	65 (34)
T2	123 (63)
T3	6 (3)
Biopsy Gleason score	
2–4	17 (9)
5–6	103 (53)
7	55 (28)
8–10	19 (10)
Prostatectomy Gleason score	
2–4	5 (3)
5–6	51 (31)
7	67 (41)
8–10	42 (25)
Prostatectomy margin status	
Unknown	25 (13)
Negative	70 (36)
Positive	99 (51)
Prostatectomy node status	
NX	31 (16)
N0	159 (82)
N1	4 (2)
Pathologic extraprostatic extension	
Unknown	69 (36)
Absent	69 (36)
Present	56 (29)
Seminal vesicle invasion	
Unknown	19 (10)
Absent	146 (75)
Present	29 (15)
Perineural invasion	
Unknown	88 (45)
Absent	14 (7)
Present	92 (48)
Pre-salvage PSA (ng/ml)	
Unknown	43 (22)
0–0.2	18 (9)
0.3–1	92 (47)
>1.0	41 (22)
Pre-salvage PSA doubling time (mos)	
Unknown	63 (32)
<12	46 (24)
>12	85 (44)

4. Discussion

Following radical prostatectomy, approximately one-third of men, despite initial favorable clinical characteristics, will develop a detectable PSA following RP [3–7]. Salvage radiotherapy represents the only potential curative option in this group of men. Even with this potential for cure, the results of an international survey of urologists revealed that 13% of respondents would recommend RT for an elevated or rising PSA 1 year after RP [26]. A previous analysis of the CaPSURE™ database of adjuvant and non-adjuvant secondary treatments indicated that less than 50% of men who undergo additional therapy after RP will receive salvage radiotherapy [27]. In this analysis of 4,563 men with clinically localized disease who underwent prostatectomy from 1989 to 2004, 237 or 5% were offered a potentially curative therapy when faced with a biochemical recurrence.

Single and multi-institutional analyses have reported the efficacy of salvage RT in preventing PSA progression [8–16]. A large number of men in this cohort, 121 (62%), experienced PSA failure subsequent to salvage RT at a median 20 months. Stephenson et al. reported similar findings as 50% of their cohort experienced PSA failure (de-

Table 2
Result of multivariable analyis with backward selection for predictors of PSA failure after salvage RT

Characteristic	Adjusted HR	95% CI	P value
Clinical T category			
T3	Reference		
T1	0.6	0.2–2.5	0.81*
T2	0.7	0.2–2.6	
Surgical Gleason score			
≥8	Reference		
2–4	0.22	0.03–1.9	0.43*
5–6	0.69	0.34–1.4	
7	0.94	0.48–1.8	
Pre-RP PSA (ng/ml)			
>20	Reference		
<4	0.88	0.3–2.7	0.80*
4.1–10	0.75	0.3–1.6	
10.1–20	0.68	0.3–1.5	
Pre-RT PSA DT (mos)			
≤12	Reference		
>12	0.68	0.42–1.2	0.13
pT3			
Absent	Reference		
Present	0.7	0.4–1.2	0.22
Pre-salvage PSA (ng/ml)			
0–0.2†	Reference		
0.2–0.3	9.0	1.13–72	0.07*
0.3–0.5	11.7	1.51–90	
0.6–1	12.6	1.70–93	
>1	15.7	2.1–117	
Mean time from RP to RT			
Continuous	1.01	1.0–1.02	0.14

HR = hazard ratio; 95% CI = 95% confidence interval.
* P value for trend.
† PSA >0 but <0.2.

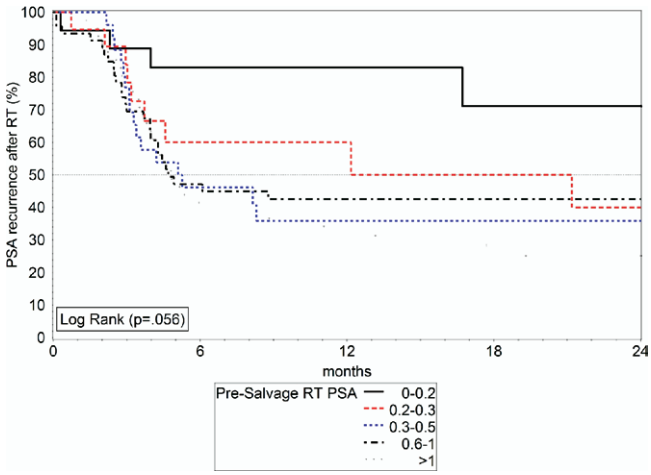

Fig. 1. PSA failure-free survival adjusted for pre-salvage RT PSA level. (Color version of figure is available online.)

fined as a value 0.1 ng/ml above the post-RT PSA nadir confirmed by a second measurement) at a median 12.5 months [14]. The number of failures, however, depends on the definition of failure. Additional analysis of this series with a failure definition of >0.4 ng/ revealed fewer failures—a decrease to 91 (47%). A definition of failure based on an absolute value may be misleading if it does not require subsequent confirmation. These findings substantiate that the presence of a detectable PSA after salvage RT does not imply a continued PSA increase, in so far as 30 of these men had a PSA of at least 0.2 ng/ml after salvage that did not reach 0.4 ng/ml. It is unclear how this finding would affect outcomes already in the literature but it suggests a potential underestimate of the efficacy of salvage RT based on the more conservative definitions of PSA failure.

Many proponents advocate that salvage RT will have its greatest benefit the earlier it is implemented. Several have reported significantly improved PSA failure-free estimates when salvage RT is employed at PSA levels of 0.6 to 2.5 [10–14,17]. The results of the univariate and multivariate analyses in this series confirm a nearly significant benefit when salvage RT is implemented at PSA levels that are lower than many already reported (Fig. 1, Table 2). The marginal significance is likely explained by the relatively small sample size of this dataset. Nevertheless, these results may suggest and prove that men with the lowest PSA levels at salvage were not likely to fail, regardless of secondary therapy. Alternatively, however, these results might indicate that earlier treatment is truly better in terms of PSA control and that adjuvant or immediate postoperative therapy potentially would be more efficacious than deferred salvage therapy.

The pre-RT PSA DT did not significantly associate with PSA failure in the initial unadjusted analysis or in the adjusted, multivariate analysis. Pre-RT PSA DT was not predictive of PSA failure when analyzed for greater than or less than 12 months or by the more specific <3 vs. 3 to 12 vs. >12 months. Two single institution series have reported significant differences in 5-year rates of PSA failure-free survival for men with pre-salvage doubling times of >11.8 and >12 months compared with shorter doubling times [20,21]. Stephenson et al. reported a PSA doubling time of ≤10 months to significantly associate with PSA failure on univariate and multivariate analyses [14]. The greatest limitation of this DT analysis and its results is inadequate power, as only two-thirds of the cohort had sufficient information to calculate a DT and subsequently be analyzed.

The attempts to stratify men into predictive groups by correlating PSA DT with the pre-RT PSA level were unfruitful and were limited by the relatively small sample size. An additional obstacle was that while the greatest benefit in salvage RT was observed for those men with the lowest pre-RT PSA levels, PSA DT calculations are limited in this situation as previously discussed. Nevertheless, this series suggests that salvage RT has its greatest potential for PSA control at the lowest pre-RT PSA levels.

Pathologic T3 disease did not significantly predict response to salvage RT. A previous report corroborates the association of penetration through the prostate capsule and durable PSA failure-free survival following salvage RT [10]. The Phase III study of immediate postoperative RT vs. observation in men with positive surgical margins or pathologic T3 disease reported by Bolla et al. included 774 men (77% of study population) with capsule perforation [22]. When the final analysis for biochemical failure-free survival was adjusted for all baseline factors, the benefit of immediate postoperative RT was highly significant for those with extracapsular extension (HR 0.50, CI 0.37–0.66, $P < 0.0001$). The composite of these data suggest the optimal benefit of radiotherapy in those with pT3 disease may be obtained in the immediate, adjuvant setting and not in the deferred, salvage setting.

Stephenson et al. developed a novel nomogram stratifying outcomes based on Gleason score, pre-RT PSA level, surgical margin status, and PSA doubling time (PSADT) [14]. Their data, incorporating 501 men, confirm that salvage RT is potentially curable, as to the PSA end-point. Buskirk et al. similarly reported a prognostic scoring system that accounts for pathologic tumor stage, Gleason score and pre-RT PSA in predicting benefit from salvage RT [16]. Our analysis, though comprised of nearly 200 men, is not able to offer a similarly predictive model. Despite the size and prospective nature of the data, its observational character limits its completeness and opens the data to biases of the participating physicians. Furthermore, this data represents patient information gathered from 65 different practices and reflects the lack of a consistent and standard practice pattern. Additionally, the information regarding salvage RT techniques is not adequate for analysis, impairing the analysis' capacity for broad and confident application. Furthermore, the absence of RT information obviates the ability to control for dose, which would certainly impact these observations, both positive and negative.

We determined that 5% of men received salvage radiotherapy for a detectable PSA postoperatively among 65 practices (mainly community-based) within the United States. PSA failure-free survival appeared to be best among men with the lowest pre-RT PSA levels, although the results only approached significance. Taken together, these results provoke the question as to what options are available to men with greater risk of PSA failure despite salvage. The long-awaited results of the Radiation Therapy Oncology Group Trial 9601, a randomized trial of salvage RT with or without 2 years of oral bicalutamide, should indicate whether a combined treatment approach in the salvage setting may prove more beneficial. Current and future studies will determine the role of chemotherapy in addition to or in place of radiotherapy, hormones, or combinations in men with PSA recurrence, particularly in those who are at the greatest risk of PSA failure despite salvage treatments.

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