Prediction of Response to Salvage Radiation Therapy in Patients With Prostate Cancer Recurrence After Radical Prostatectomy

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Purpose: **To identify factors predictive of local recurrence as defined by a complete response to salvage radiation therapy in patients whose disease recurs after radical prostatectomy.**

Patients and Methods: **Ninety-five patients with recurrence after radical prostatectomy who were evaluated by prostatic fossa biopsies, and a subset of 49 of these patients treated with radiation for control of presumed or biopsy-proven local recurrence, were studied.**

Results: **Biopsies were positive in 40 (42%) of the 95 biopsied patients. Multivariate analysis revealed that prebiopsy prostate-specific antigen (PSA) level, postrecurrence PSA doubling time, and positive digital rectal examination (DRE) of the prostatic fossa were all statistically significant predictors of a positive biopsy. For the 49 patients subsequently treated with salvage radiation therapy, the overall actuarial 3- and 5-year PSA relapse-free probabilities were 43% and 24%, respectively. Univariate analysis showed no differences in the PSA relapse-free probabilities associated with any pathologic features of the radical prostatectomy specimen, biopsy confirmation of local recurrence, or DRE of the prostatic fossa. In multivariate analysis, controlling for all other variables, preradiation PSA and postrecurrence PSA doubling time measured before radiation were the only statistically significant predictors of outcome.**

Conclusion: **DRE of the prostatic fossa, prebiopsy PSA, and postrecurrence PSA doubling time predict which patients will have biopsy-proven local recurrence. However, response to salvage radiation therapy is associated with postrecurrence PSA doubling time and with preradiation PSA level only. DRE of the prostatic fossa and biopsy confirmation of local recurrence are not associated with salvage radiation outcome.**

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UP TO ONE THIRD of patients with clinically localized prostate cancer have recurrence of the disease after radical prostatectomy,[1-3] as evidenced by postoperative elevation of serum prostate-specific antigen (PSA). Although a detectable and increasing postoperative serum PSA level is a sign of prostate cancer recurrence, it does not indicate whether the recurrence is local, systemic, or both. Current imaging technologies, including transrectal ultrasound of the prostatic fossa,[4,5] computerized tomography,[6] magnetic resonance imaging,[7] positron emission tomography,[8] and monoclonal antibody scanning,[9] still lag in their ability to detect locally recurrent prostate cancer, especially when the tumor burden is small. Clinical parameters such as digital rectal examination (DRE), prostatic fossa biopsies, time interval from radical prostatectomy to PSA recurrence, PSA doubling time, and pathologic features of the prostatectomy specimen, such as Gleason score, presence of seminal vesicle involvement, and status of surgical margins and lymph nodes,[10-13] have been suggested as guides to identify patients who were likely to have locally recurrent prostate cancer and who consequently would be better candidates for salvage local therapy.

Despite the prognostic value of many of these parameters, in retrospect, a complete and durable response to salvage radiation therapy may be the best indication of isolated locally recurrent disease. In unselected cases, the response rate after salvage radiation therapy has been reported to be as low as 10%.[14] However, in patients who have local recurrence confirmed by biopsy, response rates as high as 48% to 56% have been achieved.[15,16] The use of various clinical and pathologic parameters, short of prostatic fossa biopsies, to identify patients most likely to have locally recurrent disease, and to be best suited for salvage radiation therapy, have met with modest success. However, the clinical importance of pathologic confirmation of locally recurrent prostate cancer after radical prostatectomy by prostatic fossa biopsies for predicting the efficacy of salvage radiation remains unresolved.[17]

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The purpose of this study was to identify clinical and pathologic parameters predictive of biopsy-proven local recurrence in a group of patients with prostate cancer recurrence after radical prostatectomy, and more importantly, to determine whether any of these parameters were also predictive of salvage radiation therapy outcome.

PATIENTS AND METHODS

Patient Population and Characteristics

Between April 1985 and January 1999, a total of 95 patients who had undergone radical prostatectomy were evaluated in our department by transrectal ultrasound (TRUS) and prostatic fossa biopsies for suspected locally recurrent prostate cancer at the prostatic fossa. None of the 95 patients had clinical evidence of metastatic disease. Forty of these patients were found to harbor biopsy-proven local recurrence, whereas the remainder had isolated PSA recurrence with no pathologic evidence of local recurrence and no clinical or radiographic evidence of metastatic disease. Of the 95 patients, 50 were treated with salvage radiation therapy, 28 were treated with hormonal therapy, 12 were enrolled onto watchful waiting protocols or investigational clinical trials, and five patients were lost to follow-up. Of the 50 patients who received salvage radiation therapy, one was excluded because adjuvant investigational treatment was given before initiation of salvage radiation therapy, leaving 49 subjects who comprised the patient population of this retrospective study. Mean patient age was 67 years (median, 67; range, 53 to 83) for the 95 biopsied patients and 66.7 years (median, 67; range, 53 to 79) for the 49 patients treated with salvage radiation therapy. None of the patients received neoadjuvant treatment before radical prostatectomy or adjuvant treatment before definitive recurrence or salvage radiation therapy.

Radical prostatectomy specimens were processed by whole-mount sectioning as previously described.[18] Serum PSA levels were measured by the Hybritech Tandem-R assay (Hybritech, Inc, San Diego, CA), and a serum PSA value $\geq$ 0.4 ng/mL and increasing was considered as a detectable, sustained PSA elevation. DRE was considered abnormal if any mass, nodule, induration, or irregularity was noted at the prostatic fossa. All patients had an elevated PSA level except one who had a PSA level of 0.2 ng/mL with an abnormal DRE. The date of the first serum PSA elevation $\geq$ 0.4 ng/mL was counted as the date of postoperative biochemical recurrence, and the corresponding time interval between radical prostatectomy and first postoperative serum PSA elevation was noted for each patient. Postrecurrence serum PSA doubling time was calculated for each patient using the formula:

$$DT = \log(2) \times T/(\log[\textit{final PSA}] - \log[\textit{initial PSA}]),$$

where DT is the serum PSA doubling time, T is the time interval between the initial and final PSA level, final PSA is the preradiation PSA level, and initial PSA is the PSA level noted at the time of the postoperative biochemical recurrence. The natural logarithm was used in all logarithmic transformations.[19]

Recurrence Site Evaluation

Bone scan was negative for metastatic disease in all patients. The 95 patients underwent a total of 118 TRUS procedures, and biopsies were performed in all 95 patients. A total of 431 biopsy cores were obtained, several from each patient (median, four; range, two to eight). Patients with no visible abnormalities on the TRUS and no palpable abnormalities on DRE underwent systematic biopsies of the prostatic fossa that usually included two cores from either side of the anastomosis (one toward the bladder neck and one toward the external urethral sphincter), or, rarely, one core from each side lateral to the urethrovesical anastomosis. Patients with abnormalities palpable on DRE and no evident abnormality on TRUS underwent digitally guided biopsies and additional systematic biopsies as described above. Patients with palpable and visible abnormalities had TRUS-directed biopsies of the abnormal area, with additional directed biopsies if the visible or palpable abnormality was beyond the range of the systematic biopsies. Thirty-seven patients (76%) had a single biopsy, 11 patients (22%) had a second biopsy, and one patient (2%) had a third biopsy. Pathologic confirmation of locally recurrent prostate cancer by the prostatic fossa biopsies was demonstrated in 32 patients (65%), and only two patients had an abnormal DRE with negative prostatic fossa biopsies. One patient, after negative TRUS-guided biopsies, underwent open excisional biopsy that was found to be positive.

Salvage Radiation Therapy Technique and Follow-Up

Thirty-six (74%) of the patients were treated with external-beam radiation therapy at the Methodist Hospital (Houston, TX), and the remainder were treated at other institutions. Radiation therapy was limited to the prostatic fossa in 46 patients (94%), and three patients received pelvic radiation with an additional boost to the prostatic fossa. Radiation was delivered with 10 to 23 MV photons, and the four-fields technique (anteroposterior/posteroanterior and opposing laterals) with customized field sizes was used. Total radiation therapy dose ranged from 60 to 75.5 Gy (median, 66 Gy), delivered in daily fractions of 1.8 to 2.0 Gy. After radiation, the patients were monitored by physical examination and serum PSA measurements approximately every 3 to 6 months. Serum PSA measurements of patients who received radiation treatment in other institutions were available through regular follow-up reports.

A complete response to salvage radiation therapy was defined as the achievement and maintenance of an undetectable serum PSA level. Radiation therapy was considered to have failed in a patient if the postradiation serum PSA levels did not decrease to and remain at an undetectable level. The recommendations of the consensus panel of the American Society for Therapeutic Radiology and Oncology were followed for the definition of time of radiation failure.[20] The median follow-up of patients who had a favorable response to radiation was 29.2 months (mean, 28.6 months; range, 7.2 to 61.9 months). The median follow-up time for patients in whom salvage radiation therapy failed was 10.5 months (mean, 16.5 months; range, 2.8 to 59.5 months).

Statistical Considerations

Preoperative, prebiopsy, preradiation serum PSA values, time interval from radical prostatectomy to postoperative PSA recurrence, and postrecurrence serum PSA doubling time were considered as continuous variables in all analyses. Differences in continuous variables were tested by the Mann-Whitney test. The Pearson χ^2 test was used to compare differences between the results of the prostatic fossa biopsies relative to the results of the DRE of the prostatic fossa, as well as relative to the pathologic features of the radical prostatectomy specimen. Logistic regression analysis was used to identify clinical and pathologic features for the prediction of biopsy-proven local recurrence, with 95% confidence intervals (CIs) for the odds ratio. Serum PSA relapse after salvage radiation therapy was considered as the end point of the study. Patients with an undetectable PSA after radiation therapy were censored at the time of last follow-up. Estimates of the probability of no PSA relapse after salvage radiation therapy were calculated using the Kaplan-Meier method. Stratification of the survival

Table 1. Demographic, Preoperative, and Postoperative Clinical Data of 95 Patients With Recurrence After Radical Prostatectomy Evaluated by Prostatic Fossa Biopsies, With a Subset of 49 Patients Treated With Salvage Radiation Therapy

	Postprostatectomy Patients With Recurrence Patients (n = 95)					Salvage Radiation Patients (n = 49)	
	Prostatic Fossa Biopsy						
	No. Positive	%	No. Negative	%	*P*	No. of Patients	%
Clinical stage*							
T1a-c	11	52	10	48		11	28
T2a-b	20	33	40	67		27	69
T3a	2	67	1	33	.323	1	3
Gleason score†							
3-4	5	56	4	44		5	12
5-6	17	44	22	56		21	49
7	9	30	21	70		14	32
8-10	5	45	6	55	.541	3	7
DRE of prostatic fossa							
Positive	17	77	5	23			
Negative	23	32	50	68	< .0005		

*Clinical stage was not available in 11 of the 95 patients with prostate cancer recurrence nor in 10 of the 49 patients treated with salvage radiation therapy.
†Preoperative biopsy Gleason score was not available in six of the 95 patients with prostate cancer recurrence nor in six of the 49 patients treated with salvage radiation therapy.

function with regard to continuous variables was performed using the median value as cutoff level. Differences in the survival curves, stratified by pathologic and clinical features, were tested by the log-rank test. Univariate and multivariate Cox proportional hazards regression analyses, with 95% CIs for the hazards ratio, were used to evaluate the significance of pathologic and clinical parameters as predictors of outcome after salvage radiation therapy. Preradiation serum PSA level, postrecurrence serum PSA doubling time, and time interval from radical prostatectomy to PSA recurrence had a skewed distribution and therefore were modeled with a log transformation. Differences in the coefficients of the variables in the multivariate Cox regression analysis model were tested by Wald statistics. Spearman rank correlation was used to determine the relation between postrecurrence PSA doubling time and preradiation PSA level.

RESULTS

Clinical and Pathologic Characteristics

Of the 95 patients with recurrence after radical prostatectomy, 40 (42%) had a positive prostatic fossa biopsy. Of the 49 patients treated with salvage radiation therapy, 32 (65%) had a positive prostatic fossa biopsy. Tables 1 and 2 show the patient demographics, preradical prostatectomy parameters, and postoperative clinical and pathologic parameters in relation to the results of prostatic fossa biopsies for the 95 patients with recurrence after radical prostatectomy, as well as for the 49 patients treated with salvage radiation therapy. Patients who had biopsy-proven local recurrence had a higher prebiopsy PSA level than those with negative biopsy results (median, 2.3 ng/mL *v* 1.3 ng/mL, $P = .038$). Patients with negative prostatic fossa biopsies had a median postrecurrence PSA doubling time approximately one half that of patients with biopsy-proven local recurrence (median, 6.4 months *v* 12.2 months, $P = .008$). Patients who had a palpable abnormality in the prostatic fossa had a higher likelihood of a positive biopsy than patients with a normal DRE (77% *v* 32%, $P < .0005$).

Table 2. Demographic, Preoperative, and Postoperative Clinical Data

	Postprostatectomy Patients With Recurrence (n = 95)					Salvage Radiation Patients (n = 49)	
	Prostatic Fossa Biopsy						
	Positive		Negative				
	Median	Range	Median	Range	*P*	Median	Interquartile Range
Age, years	68	54-76	66	55-81	.485	67	53-77
Preoperative PSA, ng/mL*	8.1	3.9-63.5	9.7	2.7-42	.506	10.8	1.8-63.5
Time to PSA elevation, months	17.9	1.2-58.7	19.2	0.9-73.4	.706	19.2	0.9-53.4
Prebiopsy PSA, ng/mL	2.3	0.5-11.9	1.3	0.3-10.3	.038	—	
Preradiation PSA, ng/mL	—		—		—	2.1	0.4-11.9
Postrecurrence PSA doubling time, months	12.2	1.5-92.9	6.4	−9.3-36.8	.008	11.8	−2.0-93.6

*Preoperative PSA values were not available in seven of the 95 patients with prostate cancer recurrence nor in 3 of the 49 patients treated with salvage radiation therapy.

Table 3. Pathologic Features of 95 Patients With Recurrence After Radical Prostatectomy Evaluated by Prostatic Fossa Biopsies, With a Subset of 49 Patients Treated With Salvage Radiation Therapy

	Postprostatectomy Recurrent Patients (n = 95)					Salvage Radiation Patients (n = 49)	
	Prostatic Fossa Biopsy						
	No. Positive	%	No. Negative	%	*P*	No. of Patients	%
Pathologic stage							
pT2a-b	6	25	18	75		12	24
pT3a	23	49	24	51		24	48
pT3b	11	46	13	54	.050	13	27
RRP Gleason score*							
5-6	12	57	9	43		18	37
7	19	36	34	64		21	43
8-10	8	38	13	62	.508	10	20
Surgical margin status							
Positive	19	44	24	56		22	45
Negative	21	40	31	60	.709	27	55

*Abbreviation: RRP, radical retropubic prostatectomy specimen Gleason score.

Table 3 shows pathologic features of the radical prostatectomy specimen in relation to the results of prostatic fossa biopsies for the 95 patients with recurrence after radical prostatectomy, as well as for the subset of 49 patients treated with salvage radiation therapy. Patients with pT3 disease had a higher likelihood of a positive prostatic fossa biopsy than patients with pT2 (48% *v* 25%, $P = .050$). Thirty-four (49%) of the patients with extraprostatic extension had biopsy-proven local recurrence, whereas 19 (76%) of the patients without extraprostatic extension had a negative biopsy ($P = .033$).

Prediction of Biopsy-Proven Local Recurrence

Table 4 lists the variables evaluated in the logistic regression analysis for the prediction of biopsy-proven local recurrence. In univariate analysis, surgical margins, seminal vesicle involvement, Gleason score, and time from radical prostatectomy to first PSA elevation did not prove to be significant predictors of a positive prostatic fossa biopsy. However, extraprostatic extension, DRE of the prostatic fossa, prebiopsy PSA level, and postrecurrence PSA doubling time were all significant predictors of biopsy-proven local recurrence. In a multivariate model that included all variables, only DRE of the prostatic fossa, prebiopsy PSA level, and postrecurrence PSA doubling time were associated with positive prostatic fossa biopsy. The overall model was statistically significant ($P = .0006$), and a goodness-of-fit test demonstrated a reasonably good fit ($P = .138$). The area under the receiver-operating characteristics curve plotted for this model was calculated at 80%.

Salvage Radiation Outcome

Overall, 25 (51%) of the 49 patients who underwent salvage radiation therapy had a favorable response and maintained an undetectable postradiation serum PSA level for a median follow-up of 29.2 months. The overall actuarial 3- and 5-year serum PSA relapse-free survival rates were estimated at 43% (95% CI, 25% to 59%) and 24% (95% CI, 6% to 48%), respectively (Fig 1). Table 5 presents the differences in the PSA relapse-free probabilities stratified

Table 4. Univariate and Multivariate Logistic Regression Analyses of Clinical and Pathologic Features for the Prediction of Biopsy-Proven Local Recurrence

	Univariate			Multivariate		
Variable	Odds Ratio	*P*	95% CI	Odds Ratio	*P*	95% CI
Extraprostatic extension	2.99	.037	1.07-8.38	4.03	.059	0.95-17.17
Seminal vesicle involvement	1.27	.617	0.50-3.23	0.88	.840	0.24-3.02
Surgical margins status	1.17	.709	0.52-2.65	0.69	.488	0.21-2.09
RRP Gleason score	0.85	.482	0.53-1.35	0.78	.485	0.38-1.57
Time to PSA elevation	0.99	.464	0.97-1.01	0.99	.374	0.96-1.02
DRE of prostatic fossa	7.39	< .0005	2.43-22.49	4.74	.031	1.15-19.47
Prebiopsy PSA*	1.54	.041	1.02-2.33	2.20	.026	1.10-4.38
Postrecurrence PSA doubling time	1.04	.028	1.01-1.07	1.08	.013	1.02-1.14

*PSA values were logarithmically transformed.

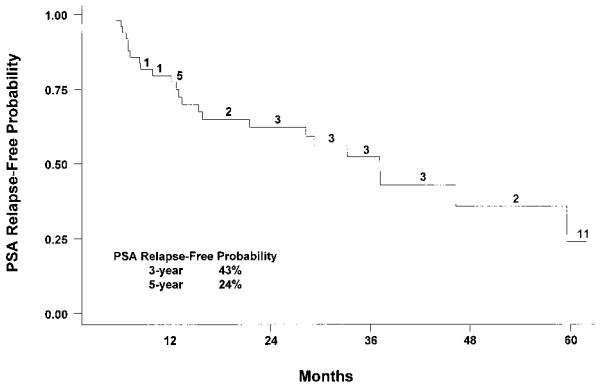

Fig 1. PSA relapse-free probability after salvage radiation therapy in patients with prostate cancer recurrence after radical prostatectomy.

by pathologic features of the radical prostatectomy specimen and clinical parameters determined at the time of recurrence. There were no significant differences in the PSA-relapse-free survival probabilities associated with any of the examined pathologic features of the radical prostatectomy specimen. Furthermore, neither biopsy confirmation of local recurrence nor results of the DRE of the prostatic fossa were associated with the outcome of salvage radiation therapy. However, when the overall median preradiation PSA level of 2.1 ng/mL was used as a cutoff value, the actuarial 5-year PSA relapse-free probability for patients with a preradiation serum PSA level < 2.1 ng/mL was 62% (95% CI, 30% to 83%), whereas the corresponding probability of patients with a preradiation PSA level ≥ 2.1 ng/mL was only 10% (95% CI, 1% to 33%) ($P = 0.001$) (Fig 2). Similarly, the actuarial 5-year PSA relapse-free survival rate for patients who had a postrecurrence serum PSA doubling time $\geq$ the overall median value of 11.8 months was 27% (95% CI, 2% to 66%), whereas the corresponding rate of patients with a doubling time less than 11.8 months was 16% (95% CI, 2% to 45%) ($P = .036$) (Fig 3).

Prediction of Response to Salvage Radiation

Univariate and multivariate Cox proportional hazards regression analyses were used for identification of outcome predictors after salvage radiation in these 49 patients (Table

Table 5. PSA Relapse-Free Probability After Salvage Radiation Therapy Stratified by Pathologic and Clinical Features

	No. of Patients	PSA-Relapse-Free Probability				
		3-Year	95% CI	5-Year	95% CI	*P*
Extraprostatic extension status						
Positive	37	39	20-58	29	10-52	.450
Negative	12	55	16-82	—	—	
Seminal vesicle involvement status						
Positive	13	29	2-68	29	2-68	.877
Negative	36	47	27-65	19	2-51	
Surgical margins status						
Positive	22	48	22-70	48	22-70	.163
Negative	27	38	15-61	—	—	
RRP Gleason score						
< 7	18	38	11-66	—	—	.746
≥ 7	31	43	22-63	32	11-56	
DRE of the prostatic fossa						
Positive	15	36	11-63	18	2-51	.662
Negative	34	46	24-66	23	2-58	
Prostatic fossa biopsy status						
Positive	32	49	28-67	27	7-54	.161
Negative	17	24	2-60	—	—	
Time to PSA elevation*						
< 19.2 months	25	28	8-52	19	3-43	.247
≥ 19.2 months	24	61	35-79	31	2-70	
Preradiation PSA value*						
< 2.1 ng/mL	24	62	30-83	62	30-83	.01
≥ 2.1 ng/mL	25	26	9-47	10	1-33	
Postrecurrence PSA doubling time*						
< 11.8 months	23†	32	13-53	16	2-45	.036
≥ 11.8 months	23†	54	19-79	27	2-66	

*Median value was used as a cutoff level.

†Three patients had identical initial and final PSA values and therefore PSA doubling time could not be determined.

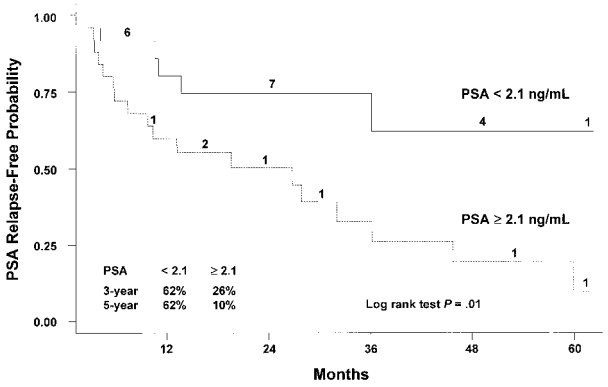

Fig 2. PSA relapse-free probability after salvage radiation therapy in patients with prostate cancer recurrence after radical prostatectomy, stratified by the median preradiation serum PSA level.

6). Predictor variables included in the model were pathologic features, such as extraprostatic extension, seminal vesicle involvement, surgical margins status, Gleason score, and status of the prostatic fossa biopsies. Clinical parameters, such as time interval from radical prostatectomy to biochemical recurrence, preradiation serum PSA level, and postrecurrence serum PSA doubling time, were also included. In univariate analysis, all examined pathologic variables, as well as pathologic confirmation of local recurrence, failed to demonstrate predictive significance (all P values $> .05$). However, preradiation serum PSA level ($P = .004$, 95% CI, 1.28 to 3.64) and postrecurrence serum PSA doubling time ($P = .001$, 95% CI, 0.19 to 0.65) were significant predictors of outcome after salvage radiation therapy. In a multivariate analysis model that included all the above mentioned variables, none of the pathologic parameters provided prognostic significance. However, after controlling for all other variables, we found that preradiation serum PSA level and postrecurrence serum PSA doubling time retained their statistical significance ($P = .025$, 95% CI, 1.16 to 8.90 and $P = .020$, 95% CI, 0.11 to 0.83, respectively) and proved to be independent predictors of outcome of salvage radiation therapy.

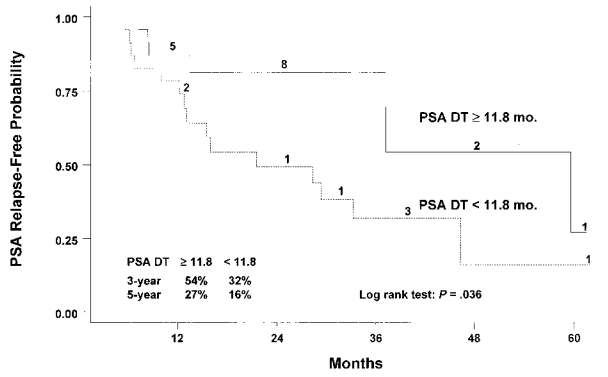

Fig 3. PSA relapse-free probability after salvage radiation therapy in patients with prostate cancer recurrence after radical prostatectomy, stratified by the median postrecurrence serum PSA doubling time.

DISCUSSION

Patients with biochemical recurrence after radical prostatectomy have a widely variable prognosis. Although some patients may remain free of clinically evident metastatic disease for a long period of time, 37% of them will develop clinical evidence of metastatic disease, and 57% of the patients who ultimately develop metastatic disease die of prostate cancer within 5 years.[21] In principle, local control of cancer should result in a decreased rate of metastatic disease and in improved survival. Several investigators have shown that locally recurrent prostate cancer may be associated with a significant risk of disease progression[22-24] and have suggested a cause-effect relationship between local recurrence and metastatic disease.[22,25,26] Therefore, locally delivered salvage radiation therapy has the potential to delay or eliminate progression in these patients. Although the reported response rate after salvage radiation therapy in unselected patients has been disappointing,[14,27] higher response rates have been reported in selected patients who were treated when the PSA level was low[28,29] and in those who had pathologically confirmed local recurrence.[15,16] Although consensus continues to grow with regard to the role of a lower preradiation PSA in the prediction of a more favorable outcome after salvage radiation therapy, controversy remains as to the role of other potential predictors of outcome, such as preoperative parameters, pathologic features of the radical prostatectomy specimen, biopsy confirmation of local recurrence before initiation of salvage radiation therapy, and PSA doubling time. Several studies have attempted to identify parameters that could predict outcome after salvage radiation therapy.

Cadeddu et al[14] recently suggested that patients with isolated PSA elevation after radical prostatectomy have a response to salvage radiation therapy similar to that of patients with local recurrence diagnosed by DRE or prostatic fossa biopsies. They concluded that there is no advantage to radiation when a patient has an isolated PSA elevation before documentation of local recurrence. However, the long-term response rate in both groups was low, ranging from 8% to 26%. In that study, patients who were treated for isolated PSA elevation had a mean PSA level of 2.2 ng/mL. Preradiation serum PSA level has been shown to be an important outcome predictor of salvage radiation therapy. Several investigators have found that a preradiation serum PSA level at a cutoff value of approximately 1.0

Table 6. Univariate and Multivariate Cox Proportional Hazards Regression Analyses for the Prediction of Salvage Radiation Therapy Outcome

Variable	Univariate			Multivariate		
	Hazards Ratio	*P*	95% CI	Hazards Ratio	*P*	95% CI
Extraprostatic extension	1.46	.452	0.54-3.92	0.53	.478	0.10-3.02
Seminal vesicle involvement	1.08	.877	0.42-2.75	1.71	.419	0.47-6.25
Surgical margins status	0.56	.169	0.24-1.28	0.89	.877	0.20-3.90
RRP Gleason score	1.01	.964	0.64-1.60	0.76	.396	0.41-1.43
Prostatic fossa biopsy status	0.53	.167	0.22-1.30	0.30	.077	0.08-1.14
DRE of prostatic fossa	1.20	.663	0.53-2.75	2.07	.233	0.63-6.80
Time to PSA elevation*	0.90	.530	0.64-1.26	0.71	.300	0.37-1.36
Preradiation PSA*	2.16	.004	1.28-3.64	3.22	.025	1.16-8.93
PSA doubling time*	0.35	.001	0.19-0.65	0.30	.020	0.11-0.83

*Continuous variables have been logarithmically transformed.

ng/mL predicts a favorable response to salvage radiation therapy,[29-33] whereas others have suggested that cutoff value to be higher, from 2.0 ng/mL[28,34] to 2.7 ng/mL,[35] or as high as 4.0 ng/mL.[15] In our study the median PSA level of patients with an undetectable PSA after salvage radiation therapy was 1.7 ng/mL (mean, 1.6 ng/mL), and the 5-year PSA relapse-free probability of patients with a preradiation PSA level less than 2.1 ng/mL was 62%. Our results, similar to the results of previous studies, also demonstrated that a low preradiation PSA level is associated with a higher probability that the patient will maintain a favorable response, regardless of the actual cutoff level, which is directly dependent on the patient population.

In previous studies, clinical stage[36] and preoperative serum PSA level[30] had both been shown to be predictive factors in univariate analysis, but in multivariate analysis, preoperative PSA did not retain its statistical significance. Pathologic features of the radical prostatectomy specimen have also been evaluated as potential predictors of outcome of salvage radiation therapy, but the results were conflicting. Pathologic stage has been reported as a significant predictor of outcome,[16,28] whereas seminal vesicle involvement has been suggested to adversely affect the response to salvage radiation.[32] Cadeddu et al[14] found that no patient with seminal vesicle involvement, Gleason score greater than 8, or lymph node metastases had an undetectable serum PSA level after salvage radiation therapy, whereas Rogers et al[15] reported that a Gleason score greater than 7 identifies patients more likely to fail salvage radiation therapy. However, other studies have failed to confirm any prognostic significance for pathologic features of the radical prostatectomy specimen.[27,30,34,35] Do et al[30] reported that, in both univariate and multivariate analyses, the only pathologic feature that predicted salvage radiation outcome was the presence of perineural invasion in the radical prostatectomy specimen. In our study, we found no association between any of the examined pathologic features and the response to salvage radiation therapy. Whether examination of additional, detailed pathologic features of the radical prostatectomy specimen, such as the presence of perineural invasion,[37] intraprostatic vascular invasion,[38] intraductal carcinoma,[39] or the expression of newer predictive molecular markers,[40] would provide additional information for the prediction of response to salvage radiation therapy remains to be determined by future studies.

The significance of pathologic confirmation of local recurrence before initiation of salvage radiation therapy remains unresolved. Lange et al[41] have reported a higher incidence of undetectable PSA levels in patients with biopsy-proven local recurrence after salvage radiation therapy than in patients with negative biopsies. In contrast, other studies have examined the role of pathologic confirmation of locally recurrent prostate cancer in the outcome of salvage radiation therapy, and have failed to demonstrate any significance.[9,42] However, the results of some of these studies were biased by the fact that as few as 13%[30] to as many as 61%[17] of the patients treated with salvage radiation therapy did not actually undergo prostatic fossa biopsies, or by the fact that a significant portion of the patients with local recurrence were diagnosed by DRE or by imaging modalities only.[35]

Our study was limited to patients who were evaluated by prostatic fossa biopsies before initiation of salvage radiation therapy. Furthermore, to minimize the false-negative rate due to sampling deficiency, several cores (mean, 3.8; range, two to eight) were obtained from each patient. Nevertheless, in univariate and multivariate analyses, biopsy confirmation of local recurrence was not a significant predictor of outcome. Certainly, some of our patients who had negative prostatic fossa biopsies also had local recurrence that remained undetected by biopsies because of low local tumor burden. Patients who harbor biopsy-detectable locally recurrent prostate cancer may have a larger local tumor that is beyond the therapeutic potential of salvage radiation.[32] It is

an accepted principle of radiation oncology that an increasing tumor burden negatively impacts disease control by radiation therapy.[43]

Time interval from radical prostatectomy to biochemical recurrence has been used in efforts to differentiate local recurrence from metastatic disease,[12] as well as to predict metastasis-free survival after biochemical recurrence.[21] Furthermore, an increased likelihood of response to salvage radiation therapy has been associated with an increased time interval from radical prostatectomy to PSA recurrence.[14] Within the follow-up period of our study, patients whose salvage radiation therapy failed had a shorter median time interval from radical prostatectomy to biochemical recurrence than did patients who had a favorable outcome after salvage radiation therapy (15.8 months *v* 27.2 months, respectively). However, in multivariate analysis, time interval from radical prostatectomy to biochemical recurrence had no prognostic significance. These results are consistent with the results of other studies.[15,30]

We also examined postrecurrence serum PSA doubling time as a variable in all analyses in our study. Previously, both Wu et al[34] and Forman et al[36] failed to demonstrate any significant value of PSA doubling time for the prediction of the results of salvage radiation therapy. In contrast, we found that postrecurrence serum PSA doubling time is an important feature in patients treated with salvage radiation therapy. Patients who maintained an undetectable serum PSA level after salvage radiation therapy for the duration of the follow-up period had a median PSA doubling time that was almost twice the PSA doubling time of patients who relapsed (18.1 months *v* 9.0 months, respectively).

Recent studies suggest that serum PSA doubling time is an important clinical feature of prostate cancer in other clinical settings.[19] PSA doubling time has been used in monitoring disease progression in untreated prostate cancer patients,[44,45] as well as in the prediction of clinical relapse and type of recurrence after external radiation therapy for the treatment of prostate cancer.[46-49] After surgery, within the clinical scenario of a biochemical recurrence, serum PSA doubling time has been shown to correlate with the site of the recurrence, which thus facilitates clinical decision-making in these patients. Trapasso et al[13] reported that metastatic disease was associated with a median PSA doubling time of 4.3 months in patients with biochemical recurrence after radical prostatectomy, whereas patients with local recurrence or PSA elevation had only a median PSA doubling time of 11.7 months. Similarly, Patel et al[11] have shown that a PSA doubling time greater than 6 months is more likely to be associated with local recurrence than with metastatic disease, and Pound et al[21] demonstrated that a PSA doubling time at a cutoff level of 10 months can help predict the likelihood of development of metastatic disease.

In our study, preradiation serum PSA level and postrecurrence serum PSA doubling time were inversely related (Spearman's rho, -0.32; $P = .032$), and both parameters independently predicted outcome. Patients who had a rapid serum PSA doubling time ($<$ the median of 11.8 months) and a high preradiation PSA ($\geq$ the median of 2.1 ng/mL) had a 3-year PSA-relapse-free probability of only 8%. However, in patients with a rapid PSA doubling time but a low preradiation PSA ($<$ 2.1 ng/mL), the corresponding probability was 75% ($P = .002$). These results indicate that salvage radiation therapy might not be appropriate for patients with a rapid PSA doubling time and a high serum PSA level after radical prostatectomy. However, although a rapid postrecurrence PSA doubling time is associated in general with a poorer response to salvage radiation therapy, at least a portion of the patients with rapid PSA doubling time may be expected to respond to salvage radiation therapy, if treatment is initiated early enough, when the PSA level is relatively low.

We studied predictors of efficacy in patients with biochemical recurrence after radical prostatectomy. The role of adjuvant radiation therapy after radical prostatectomy, in patients selected on the basis of adverse pathologic features such as positive surgical margins or extraprostatic extension, remains unresolved. Several studies have demonstrated an increased rate of control of local recurrence in patients who receive adjuvant radiation therapy; however, improvement in the survival rate of these patients has not been demonstrated.[50-52] Furthermore, depending on the selection criteria for the administration of adjuvant radiation therapy, a significant proportion of these patients, in the range of 30% to 70%, may be exposed unnecessarily to the potential complications and cost of this treatment, because they may never experience recurrence after radical prostatectomy.[36,50,53,54] Our study suggests that the use of radiation therapy to treat recurrence in patients with longer PSA doubling time and low PSA, rather than the use of it in an adjuvant setting, still leads to a high response rate.

Our results are somewhat limited by the retrospective nature of the study, as well as by patient selection bias, because not all patients originally evaluated by prostatic fossa biopsies for evidence of locally recurrent prostate were subsequently treated with salvage radiation therapy. Although in concordance with Lightner et al[55] we found that the detection rate of local recurrence by prostatic fossa biopsies was 42%, 65% of the patients treated with salvage radiation therapy had a positive biopsy, indicating a potential bias toward the treatment of patients with biopsy-proven local recurrence. Finally, although the median follow-up of

our study is similar to that reported by other studies, it is likely that with longer follow-up the number of favorable outcomes may decrease.

Outcome of salvage radiation therapy can be independently predicted by postrecurrence serum PSA doubling time, as well as by preradiation serum PSA level. The parameters can be used in combination to direct clinical decision-making in patients in whom radical prostatectomy has failed. Although these two parameters are predictive of prostatic fossa biopsy results, biopsy confirmation of local recurrence does not seem to provide significant additional prognostic information with regard to outcome of salvage radiation therapy when the PSA and the PSA doubling time are known. Postrecurrence serum PSA doubling time can be readily determined before local tumor burden exceeds the therapeutic capability of salvage radiation therapy. Ultimately a multi-institutional trial would allow verification of our results and potentially lead to the development of a clinically useful nomogram.

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