



Online article and related content
current as of July 12, 2009.

Salvage Radiotherapy for Recurrent Prostate Cancer After Radical Prostatectomy

Andrew J. Stephenson; Shahrokh F. Shariat; Michael J. Zelefsky; et al.

JAMA. 2004;291(11):1325-1332 (doi:10.1001/jama.291.11.1325)

<http://jama.ama-assn.org/cgi/content/full/291/11/1325>

Correction

[Contact me if this article is corrected.](#)

Citations

[This article has been cited 192 times.](#)
[Contact me when this article is cited.](#)

Topic collections

Men's Health; Prostate Disease; Oncology; Prostate Cancer; Radiation Therapy;
Urology
[Contact me when new articles are published in these topic areas.](#)

Related Articles published in
the same issue

Salvage Radiotherapy for Recurrent Prostate Cancer: The Earlier the Better
[Mitchell S. Anscher. *JAMA*. 2004;291\(11\):1380.](#)

Related Letters

Use and Timing of Radiotherapy in High-Risk Prostate Cancer
[John F. Ward et al. *JAMA*. 2004;291\(23\):2817.](#)

In Reply:

[Andrew J. Stephenson et al. *JAMA*. 2004;291\(23\):2817.](#)
[Mitchell S. Anscher. *JAMA*. 2004;291\(23\):2818.](#)

Subscribe

<http://jama.com/subscribe>

Permissions

permissions@ama-assn.org
<http://pubs.ama-assn.org/misc/permissions.dtl>

Email Alerts

<http://jamaarchives.com/alerts>

Reprints/E-prints

reprints@ama-assn.org

Salvage Radiotherapy for Recurrent Prostate Cancer After Radical Prostatectomy

Andrew J. Stephenson, MD

Shahrokh F. Shariat, MD

Michael J. Zelefsky, MD

Michael W. Kattan, PhD

E. Brian Butler, MD

Bin S. Teh, MD

Eric A. Klein, MD

Patrick A. Kupelian, MD

Claus G. Roehrborn, MD

David A. Pistenmaa, MD

Heather D. Pacholke, MD

Stanley L. Liauw, MD

Matthew S. Katz, MD

Steven A. Leibel, MD

Peter T. Scardino, MD

Kevin M. Slawin, MD

APPROXIMATELY 30 000 MEN ANNUALLY in the United States will have recurrence of prostate cancer after radical prostatectomy.¹ Initially, for most of these patients the only evidence of recurrent disease is an increasing serum prostate-specific antigen (PSA) level without radiographic or physical evidence of disease. An estimated 65% of these men will develop bone metastases within 10 years in the absence of salvage therapy.² A rapid PSA doubling time (PSADT), high-grade disease, and a short disease-free interval after radical prostatectomy are prognostic factors associated with the development of metastases in untreated patients with an increasing PSA level.²⁻⁴ However, some patients with an increasing PSA level will have disease initially

Context Salvage radiotherapy may potentially cure patients with disease recurrence after radical prostatectomy, but previous evidence has suggested that it is ineffective in patients at the highest risk of metastatic disease progression.

Objective To delineate patients who may benefit from salvage radiotherapy for prostate cancer recurrence by identifying variables associated with a durable response.

Design, Setting, and Patients Retrospective review of a cohort of 501 patients at 5 US academic tertiary referral centers who received salvage radiotherapy between June 1987 and November 2002 for detectable and increasing prostate-specific antigen (PSA) levels after radical prostatectomy.

Main Outcome Measure Disease progression after salvage radiotherapy, defined as a serum PSA value ≥ 0.1 ng/mL above the postradiotherapy PSA nadir confirmed by a second PSA measurement that was higher than the first by any amount, by a continued increase in PSA level after treatment, or by the initiation of androgen deprivation therapy after treatment.

Results Over a median follow-up of 45 months, 250 patients (50%) experienced disease progression after treatment, 49 (10%) developed distant metastases, 20 (4%) died from prostate cancer, and 21 (4%) died from other or unknown causes. The 4-year progression-free probability (PFP) was 45% (95% confidence interval [CI], 40%-50%). By multivariable analysis, predictors of progression were Gleason score of 8 to 10 (hazard ratio [HR], 2.6; 95% CI, 1.7-4.1; $P < .001$), preradiotherapy PSA level greater than 2.0 ng/mL (HR, 2.3; 95% CI, 1.7-3.2; $P < .001$), negative surgical margins (HR, 1.9; 95% CI, 1.4-2.5; $P < .001$), PSA doubling time (PSADT) of 10 months or less (HR, 1.7; 95% CI, 1.2-2.2; $P = .001$), and seminal vesicle invasion (HR, 1.4; 95% CI, 1.1-1.9; $P = .02$). Patients with no adverse features had a 4-year PFP of 77% (95% CI, 64%-91%). When treatment was given for early recurrence (PSA level ≤ 2.0 ng/mL), patients with Gleason scores of 4 to 7 and a rapid PSADT had a 4-year PFP of 64% (95% CI, 51%-76%) and of 22% (95% CI, 6%-38%) when the surgical margins were positive and negative, respectively. Patients with Gleason scores of 8 to 10, positive margins, and receiving early salvage radiotherapy had a 4-year PFP of 81% (95% CI, 57%-100%) when the PSADT was longer than 10 months and of 37% (95% CI, 16%-58%) when the PSADT was 10 months or less.

Conclusions Gleason score, preradiotherapy PSA level, surgical margins, PSADT, and seminal vesicle invasion are prognostic variables for a durable response to salvage radiotherapy. Selected patients with high-grade disease and/or a rapid PSADT who were previously thought to be destined to develop progressive metastatic disease may achieve a durable response to salvage radiotherapy.

JAMA. 2004;291:1325-1332

www.jama.com

confined to the pelvis that subsequently may give rise to distant metastases. Isolated local relapse potentially can be cured by salvage radiotherapy, but there is no proven cure for metastatic disease.

Complicating the treatment of these patients is the inability to distinguish

patients with an isolated local recurrence from those with occult distant metastases, who are unlikely to ben-

Author Affiliations are listed at the end of this article.
Corresponding Author: Kevin M. Slawin, MD, Scott Department of Urology, Baylor College of Medicine, 6535 Fannin St, Suite 2100, Houston, TX 77030 (kslawin@bcm.tmc.edu).

For editorial comment see p 1380.

Table 1. Baseline Clinical Characteristics of 501 Patients Undergoing Salvage Radiotherapy for Detectable and Increasing PSA Levels After Radical Prostatectomy

Characteristic	No. (%) [*]
Total No. of patients	501
Preprostatectomy age, mean (SD) [range], y	62.3 (6.7) [40-79]
Preprostatectomy PSA level, median (range), ng/mL	9.8 (2-248)
Preprostatectomy neoadjuvant androgen deprivation therapy	55 (11)
Gleason score [†]	
4-6	101 (20)
7	264 (53)
8-10	114 (23)
Preradiotherapy PSA level, median (range), ng/mL	0.72 (0.1-26)
Positive surgical margins	268 (54)
PSA doubling time, median (range), mo	7.4 (1-269)
Seminal vesicle invasion	139 (28)
Extracapsular extension	282 (56)
Positive lymph nodes	14 (3)
Disease-free interval, median (range), mo	9.7 (0-138)
Persistent detectable PSA level after radical prostatectomy	160 (32)
Neoadjuvant androgen deprivation therapy prior to salvage radiotherapy	83 (17)
Radiation dose, median (range), rad	6480 (3780-7560)
Follow-up after radical prostatectomy, median (range), mo	81 (5-192)
Follow-up after radiotherapy, median (range), mo	45 (1-180)

Abbreviation: PSA, prostate-specific antigen.
 SI conversion factor: To convert rad to Gy, multiply rad values by 0.01.
^{*}Except where otherwise indicated.
[†]Range of scale for Gleason Score is 2-10; however, no patients in this study had scores of 2 or 3.

efit from salvage radiotherapy. Current imaging modalities lack the specificity and sensitivity to identify loco-regional disease, especially early in the course of recurrence, when the cancer burden is lowest but most amenable to therapy.^{1,5} Bone scintigraphy is not sufficiently sensitive to rule out the presence of metastases because lesions usually are not detectable at serum PSA levels less than 10 ng/mL.^{6,7}

In contrast with the results of primary radiotherapy for localized prostate cancer,^{8,9} the reported success rates of salvage radiotherapy range between 10% and 50%, suggesting that the majority of unselected patients with an increasing PSA level have occult metastases and do not benefit from salvage radiotherapy.¹⁰⁻²⁴ In single-institution studies, conflicting evidence has been reported¹⁰⁻¹² regarding the association of preradiotherapy PSA level, negative surgical margins, PSADT, and pathological stage with a durable response to salvage radiotherapy. However, the small patient numbers and resulting low statistical power of these and similar

studies have limited investigators' ability to identify prognostic variables. Recognizing these limitations, we conducted a multicenter analysis of the outcome of salvage radiotherapy in a cohort of patients with recurrence of prostate cancer after radical prostatectomy to identify variables that are associated with a durable response.

METHODS

Patients

Between 1987 and 2002, 501 patients with disease recurrence after radical prostatectomy underwent salvage radiotherapy at 1 of 5 participating academic tertiary referral centers. Data were obtained from each institution's institutional review board-approved prospective clinical prostate cancer research database after obtaining written patient consent or from a retrospective review of the medical records. Retrospectively acquired data were deidentified according to Health Insurance Portability and Accountability Act (HIPAA) guidelines. The clinical characteristics at the time of salvage radiotherapy are

listed in TABLE 1. Because several patients underwent radical prostatectomy at an outside institution, the method by which the pathological specimens were processed was not available for all patients. No patient had received any adjuvant therapy after radical prostatectomy before receiving either salvage radiotherapy or neoadjuvant androgen deprivation therapy (ADT).

Prior to salvage radiotherapy, 481 patients (96%) had a serum PSA level of 0.2 ng/mL or greater confirmed by a second PSA measurement that was higher than the first by any amount. Twenty patients (4%) received treatment before the PSA level reached 0.2 ng/mL but had at least 2 consecutive PSA increases at levels of 0.10 ng/mL or more. All patients were believed by their treating physician to have isolated local recurrence at the time of salvage radiotherapy. Biopsy-confirmed local recurrence was documented in 105 patients (21%). A persistent detectable PSA level after radical prostatectomy was present in 160 patients (32%). The PSADT was calculated for each patient using all nonzero PSA values after radical prostatectomy until the start of salvage radiotherapy or neoadjuvant ADT using the slope from the linear regression of the natural log of the patient's PSA level vs time of PSA measurement in months. The PSADT was estimated as 0.693 divided by the slope.²

Eighty-three patients (17%) received neoadjuvant ADT prior to salvage radiotherapy for a median duration of 3 months (range, 1-6). Radiation was delivered to the prostatic fossa by a variety of techniques, including a 4-field technique, 6-field conformal technique, and 5-field intensity-modulated radiotherapy approach, in daily fractions of 180 to 200 rad (1.8-2.0 Gy) using 10- to 23-MV photons. Twenty-four patients (5%) received radiation to pelvic lymph nodes. The median radiation dose was 6480 rad (64.8 Gy) (range, 3780-7560 rad [37.8-75.6 Gy]); 6 patients (1.1%) received doses less than 5940 rad (59.4 Gy) and 65 patients (13%) received doses greater than 7000 rad (70 Gy).

After salvage radiotherapy, patients were monitored for disease recurrence with serial measurements of PSA level and imaging studies as indicated. A complete response to treatment was defined as the achievement of a PSA nadir of 0.10 ng/mL or less. Progression of PSA was defined as a serum PSA value of 0.1 ng/mL or more above the postradiotherapy PSA nadir confirmed by a second PSA measurement that was higher than the first by any amount, by a continued increase in PSA level after treatment, or by the initiation of ADT after treatment.

Statistical Analysis

Overall survival, disease-specific survival, and progression-free probability (PFP) were estimated using the Kaplan-Meier method. Patients were censored from the PSA progression analysis if they were lost to follow-up or died from causes other than prostate cancer. In all analyses, preradiotherapy PSA level and PSADT were analyzed as categorical variables using predetermined cutoff values identified from the literature. Numerous cut points have been reported in the literature for presalvage radiotherapy PSA level between 0.6 and 4.0 ng/mL.^{10,11,18} For this study, PSA level was categorized as 1.0 ng/mL or lower, 1.1 through 2.0 ng/mL, and greater than 2.0 ng/mL to evaluate the prognostic significance of low, intermediate, and high preradiotherapy levels.²⁵ Pound et al² have reported that a PSADT of 10 months identifies patients who are at higher risk of developing distant metastases. Cox proportional hazards regression analysis was used to determine the association of variables with a durable response to salvage radiotherapy in univariate and multivariable analyses. For all analyses, the level of significance was set at .05. Statistical analysis was performed using SPSS version 10.0 (SPSS Inc, Chicago, Ill).

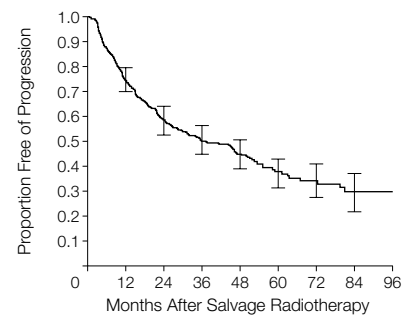
RESULTS

Over a median follow-up of 45 months, 250 of the 501 patients (50%) experi-

enced disease progression after treatment, 49 (10%) developed distant metastases, 20 (4%) died from prostate cancer, and 21 (4%) died from other or unknown causes. The 7-year actuarial disease-specific and overall survival was 90% (95% confidence interval [CI], 86%-95%) and 82% (95% CI, 76%-88%), respectively. A total of 339 patients (67%) achieved a complete response to salvage radiotherapy with or without neoadjuvant ADT. The 4-year PFP after salvage radiotherapy was 45% (95% CI, 40%-50%) (FIGURE 1). Of the patients who experienced PSA progression after salvage radiotherapy, the median time to progression was 12.5 months and 92% of these patients experienced progression within 4 years.

The following preradiotherapy variables were significant predictors of PSA progression after salvage radiotherapy in univariate analyses: PSA level before radical prostatectomy ($P = .04$), Gleason score ($P < .001$), preradiotherapy PSA level ($P < .001$), negative surgical margins ($P = .002$), PSADT of 10 months or less ($P < .001$), seminal vesicle invasion ($P < .001$), and persistent detectable PSA level after radical prostatectomy ($P = .005$) (TABLE 2). There was no significant difference between the progression rates for patients with a preradiotherapy PSA level of 1.0 ng/mL or less and of 1.1 through 2.0 ng/mL ($P = .22$). However, a PSA level greater than 2.0 ng/mL was associated with a higher progression rate than was a level between 1.1 and 2.0 ng/mL ($P < .001$). Patients with a Gleason score of 7 had an intermediate prognosis compared with those with a Gleason score of 4 to 6 ($P = .03$) and those with a score of 8 to 10 ($P < .001$). A disease-free interval of 12 months or less after radical prostatectomy, extracapsular extension, neoadjuvant ADT, and radiation dose greater than 6480 rad (64.8 Gy) were not associated with the PSA outcome. Positive lymph nodes were not associated with disease progression, but only 1 patient with lymph node involvement has been followed up for more than 3 years without recurrence.

Figure 1. Kaplan-Meier Estimate of Progression-Free Probability After Salvage Radiotherapy



No. at Risk 501 333 232 145 99 56 27 15

Error bars indicate 95% confidence intervals.

In a multivariable analysis, PSA progression was associated with Gleason score of 8 to 10 ($P < .001$), preradiotherapy PSA level greater than 2.0 ng/mL ($P < .001$), negative surgical margins ($P < .001$), PSADT of 10 months or less ($P = .001$), and seminal vesicle invasion ($P = .02$) (TABLE 3). A Gleason score of 7 and a PSA level of 1.1 through 2.0 ng/mL did not significantly influence the progression rate compared with a Gleason score of 4 to 6 ($P = .06$) and a PSA level of 1.0 ng/mL or less ($P = .31$), respectively. Given that a preradiotherapy PSA level of 1.1 through 2.0 ng/mL was not associated with a worse outcome than a PSA level of 1.0 ng/mL or less in the multivariable analysis, we analyzed the prognostic significance of very low PSA thresholds (PSA level ≤ 0.6 ng/mL) proposed by Katz et al.¹¹ Patients with a preradiotherapy PSA level of 0.6 ng/mL or less had a better prognosis than those with a level between 0.61 and 2.0 ng/mL (hazard ratio, 1.6; 95% CI, 1.2-2.2; Bonferroni-corrected $P = .006$) or a PSA greater than 2.0 ng/mL (hazard ratio, 2.8; 95% CI, 2.0-4.0; Bonferroni-corrected $P < .001$) when other variables were considered and when adjusted for multiple hypothesis testing.

In a cohort of 356 patients who received no neoadjuvant ADT and for whom complete data were available for Gleason score, preradiotherapy PSA level, surgical margins, and PSADT, the 4-year

actuarial PFP was stratified by each of the variables (FIGURE 2). Patients with no adverse features had a 4-year PFP of 77%. When patients received early salvage radiotherapy (pretreatment PSA level ≤ 2.0 ng/mL), those with Gleason scores of 4 to 7 and a rapid PSADT had a 4-year PFP of 64% and 22% when the surgical mar-

gins were positive and negative, respectively. Patients with positive margins and Gleason scores of 8 to 10 receiving early salvage radiotherapy had a 4-year PFP of 81% when the PSADT was greater than 10 months and 37% when it was 10 months or less. Patients who received late salvage radiotherapy (pretreatment PSA

level > 2.0 ng/mL) had an overall 4-year PFP of 20%, and the Gleason score, surgical margin status, and PSADT did not significantly influence the outcome.

COMMENT

For patients with recurrent prostate cancer after radical prostatectomy, salvage radiotherapy remains the only potentially curative therapy. However, results from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) longitudinal registry indicate that less than 50% of patients who receive secondary treatment after radical prostatectomy will undergo salvage radiotherapy.²⁶ The majority will receive ADT, a treatment that offers no hope for cure. Patients with high-grade disease, a rapidly increasing PSA level, and a short disease-free interval after radical prostatectomy are at the highest risk for progression to distant metastases.² Urologists may be reluctant to treat patients with salvage radiotherapy because previous studies have reported that it is ineffective for cancers with these aggressive features. There is also a widespread perception that the majority of patients with PSA recurrence have occult metastatic disease, precluding successful local salvage therapy.²⁷

We conducted a multicenter analysis of 501 patients undergoing salvage radiotherapy for an increasing PSA level after radical prostatectomy in order to reliably identify prognostic variables associated with a durable response. In this cohort, a Gleason score of 8 to 10, pre-radiotherapy PSA level greater than 2.0 ng/mL, negative surgical margins, PSADT of 10 months or less, and seminal vesicle invasion were significant predictors of disease progression despite salvage radiotherapy. Yet we demonstrated that subsets of patients with high-grade disease and/or a rapid PSADT who were thought to be incurable could still achieve a durable response to salvage radiotherapy when the treatment was administered early in the course of recurrent disease. These results suggest that salvage radiotherapy may prevent metastatic disease progression for those patients at the highest risk.

Table 2. Univariate Analysis of Variables Associated With Freedom From PSA Progression After Salvage Radiotherapy

Variable	4-Year Progression-Free Probability, % (95% CI)	Median Progression-Free Time, mo (95% CI)	P Value*
Preprostatectomy PSA level, ng/mL			.04
≤ 10	53 (46-60)	55 (38-72)	
> 10	39 (32-46)	32 (22-41)	
Gleason score			$< .001$
4-6	67 (56-78)	67 (54-81)	
7	44 (37-52)	38 (27-48)	
8-10	27 (18-36)	17 (12-22)	
Peradiotherapy PSA level, ng/mL			$< .001$
≤ 1.0	53 (46-60)	52 (43-61)	
1.1-2.0	49 (38-61)	35 (3-68)	
> 2.0	21 (12-29)	15 (10-21)	
Surgical margins			.002
Positive	53 (46-60)	53 (39-67)	
Negative	34 (26-42)	24 (17-31)	
PSA doubling time, mo			$< .001$
> 10	58 (50-67)	64 (45-83)	
≤ 10	36 (29-43)	27 (20-34)	
Seminal vesicle invasion			$< .001$
Absent	52 (45-58)	52 (42-61)	
Present	27 (19-36)	18 (14-23)	
Extracapsular extension			.07
Absent	51 (42-60)	50 (31-69)	
Present	41 (34-47)	32 (21-42)	
Lymph node involvement			.12
Negative	45 (40-51)	41 (31-51)	
Positive	18 (0-47)	13 (3-23)	
Disease-free interval, mo			.31
> 12	49 (40-57)	46 (29-63)	
≤ 12	42 (36-49)	32 (20-43)	
PSA level after radical prostatectomy			.005
Undetectable	50 (43-56)	46 (36-56)	
Detectable	36 (28-44)	25 (18-32)	
Neoadjuvant androgen deprivation therapy prior to salvage radiotherapy			.77
No	46 (40-51)	41 (30-52)	
Yes	39 (26-52)	32 (21-44)	
Radiotherapy dose, rad			.24
> 6480	47 (39-55)	46 (29-63)	
≤ 6480	44 (37-51)	37 (25-49)	

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

SI conversion factor: To convert rad to Gy, multiply rad values by 0.01.

*P values relate to Kaplan-Meier estimates of freedom from progression, as determined by log-rank test.

Numerous studies have demonstrated better outcomes with salvage radiotherapy when it is administered at the earliest evidence of disease progression, ie, when PSA has just begun to increase above detectable levels. A high preradiotherapy PSA level has consistently been shown to negatively influence the outcome of patients undergoing salvage radiotherapy. Studies have proposed preradiotherapy PSA cut points from 0.6 to 4.0 ng/mL for predicting the most favorable response to salvage radiotherapy.^{10,11,13,15,16,18} The American Society for Therapeutic Radiology and Oncology (ASTRO) consensus panel concluded that the appropriate PSA cut point "seemed to be 1.5 ng/mL" based on the available evidence.²⁵ In our multivariable analysis, only preradiotherapy PSA level greater than 2.0 ng/mL had a significant association with progression after salvage radiotherapy. However, patients receiving treatment at very low PSA levels (≤ 0.6 ng/mL) had an improved outcome compared with patients with a preradiotherapy PSA level between 0.61 and 2.0 ng/mL when other variables were considered and when corrected for multiple hypothesis testing. The use of very low PSA thresholds risks overtreating patients whose PSA level is detectable due to residual benign prostatic tissue. For example, one recent report demonstrated that a single PSA elevation of less than 0.4 ng/mL after radical prostatectomy is associated with subsequent stable, nonprogressing disease in up to 50% of patients.²⁸ Thus, while outcomes are better when salvage radiotherapy is administered earlier in the course of recurrent disease, physicians should avoid the risk of overtreatment by confirming a trend of increasing serum PSA levels rather than simply relying on a single PSA cut point to establish clinically significant disease recurrence.

The identification of high-grade disease and a rapid PSADT as risk factors for disease progression after salvage radiotherapy is consistent with the observed association of these variables with the development of metastatic dis-

Table 3. Multivariable Cox Regression Analysis of Predictors of PSA Progression After Salvage Radiotherapy

Predictor	HR (95% CI)	P Value
Preprostatectomy PSA level >10 ng/mL	1.1 (0.8-1.4)	.73
Gleason score		
4-6	Reference	
7	1.5 (0.98-2.2)	.06
8-10	2.6 (1.7-4.1)	<.001
Preradiotherapy PSA level, ng/mL		
≤ 1.0	Reference	
1.1-2.0	1.2 (0.8-1.7)	.31
>2.0	2.3 (1.7-3.2)	<.001
Negative surgical margins	1.9 (1.4-2.5)	<.001
PSA doubling time ≤ 10 mo	1.7 (1.2-2.2)	.001
Seminal vesicle invasion	1.4 (1.1-1.9)	.02
Extracapsular extension	1.2 (0.9-1.6)	.21
Positive lymph nodes	1.5 (0.7-3.0)	.32
Disease-free interval ≤ 12 mo	1.0 (0.7-1.3)	.71
Neoadjuvant androgen deprivation therapy prior to salvage radiotherapy	0.8 (0.5-1.1)	.16
Radiation dose <6480 rad	1.0 (0.7-1.3)	.96

Abbreviations: CI, confidence interval; HR, hazard ratio; PSA, prostate-specific antigen. SI conversion factor: To convert rad to Gy, multiply rad values by 0.01.

ease in cohorts of patients treated with radical prostatectomy and with primary radiotherapy.^{2-4,29,30} Tumors with these features are more likely to metastasize early in the course of the disease (either before radical prostatectomy or from residual pelvic disease).

We confirmed our previous observation that positive surgical margins are a powerful predictor of a durable response to salvage radiotherapy.^{10,11} A positive surgical margin suggests a greater likelihood that recurrence is due to residual pelvic disease. Therefore, a patient with positive margins who relapses is more likely to benefit from salvage radiotherapy than a patient with negative margins, whose PSA level is more likely to represent distant disease. Rates of positive surgical margins have been reported in 5% to 53% of patients undergoing radical prostatectomy.³¹⁻³³ While the risk of positive surgical margins generated at radical prostatectomy is associated with adverse clinical and pathological features of prostate cancer, the surgeon's technique appears to be the most significant parameter controlling the status of surgical margins.³⁴ Furthermore, positive surgical margins have been demonstrated to be an important

predictor of disease recurrence after radical prostatectomy.³¹ Our results further establish that disease recurrence in the presence of positive surgical margins often represents local recurrence, even for patients with aggressive features such as a Gleason score of 8 to 10 or a rapid PSADT.

We could not demonstrate the significance of positive lymph nodes for disease progression after salvage radiotherapy, perhaps because the number of patients with positive nodes was low. However, only 1 patient with positive lymph nodes has been followed up for more than 3 years without relapse. We believe that positive lymph nodes are an indicator of systemic disease and that patients with nodal disease are unlikely to benefit from additional local therapy.

Unlike previous studies, this study did not identify an association between the use of neoadjuvant ADT or radiation dose and the success of salvage radiotherapy.^{11,14,15,20,21} However, the high durable response rates observed in our study were achieved using radiation doses comparatively lower than doses currently administered safely by intensity-modulated technology. A higher radiation dose may be beneficial for these patients, as has been demonstrated in

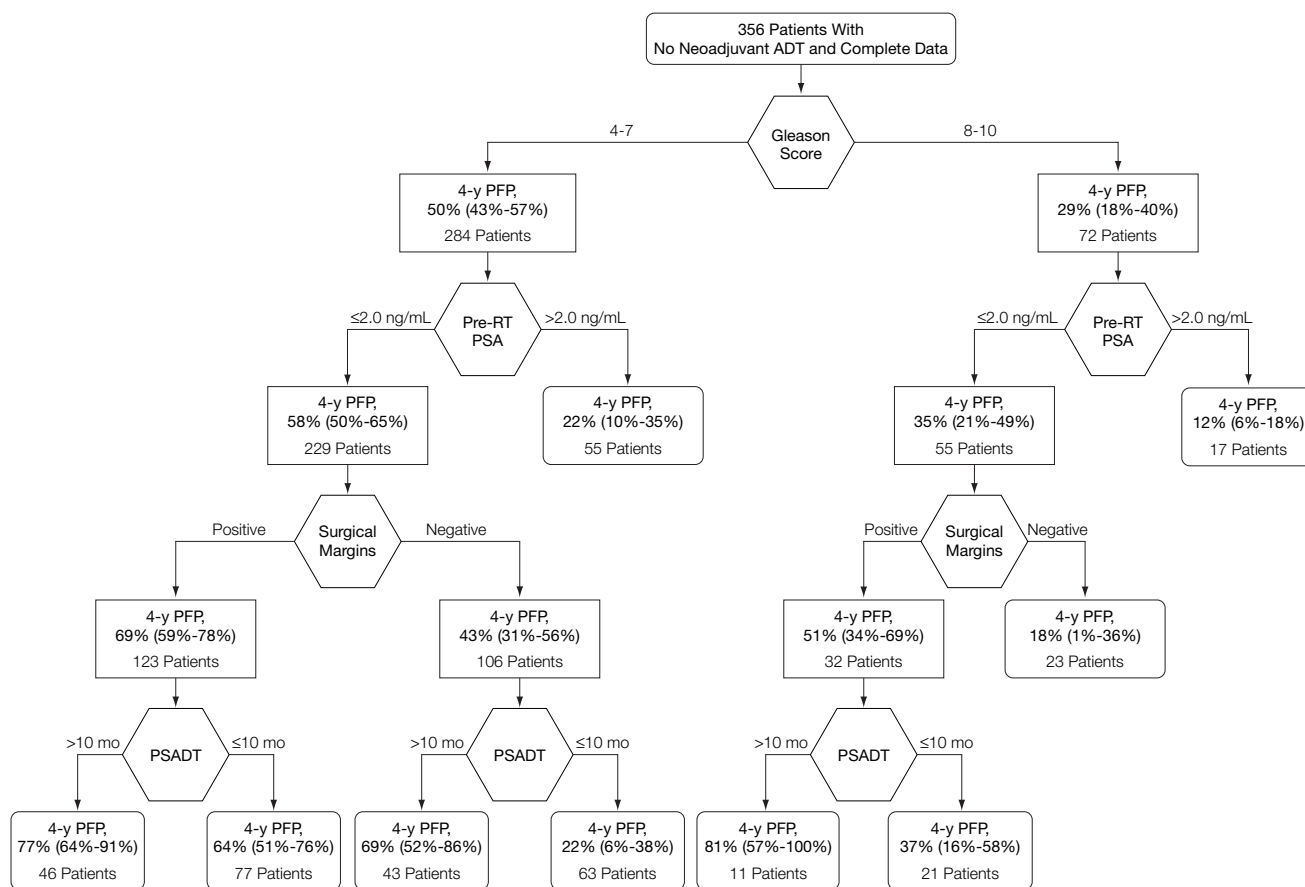
patients treated with primary radiotherapy,³⁵ but clinical trials would be required to test this hypothesis.

To identify subgroups of patients who are most likely to benefit from salvage radiotherapy, we stratified the outcome using Gleason score, preradiotherapy PSA level, surgical margin status, and PSADT. Overall, patients with a Gleason score of 4 to 7 and a slow PSADT (<10 months) had a 4-year PFP greater than 70% when radiation was delivered early, when the PSA level was lower. A significant proportion of selected patients with adverse features known to be associated with metastatic disease may nevertheless achieve a durable response to salvage radiotherapy. For patients with Gleason

scores of 4 to 7 and a rapid PSADT, 67% will have a durable response to early salvage radiotherapy if they have positive surgical margins, compared with 22% for those having negative margins. Likewise, more than half of patients with Gleason scores of 8 to 10 and positive margins will achieve a durable response to salvage radiotherapy, and over one third of these patients with a rapid PSADT will be free of disease at 4 years. These results have important implications for patients with recurrent prostate cancer, as it has been generally believed that high-grade disease and a rapidly increasing PSA level signify the presence of distant metastases, precluding successful local salvage therapy.

Given the insensitivity of current imaging modalities, a durable response to salvage radiotherapy may be the most accurate means of identifying isolated local recurrence. The incidence and clinical characteristics of locally recurrent prostate cancer can thus be inferred from patients who achieve a durable response to salvage radiotherapy. The findings of our study run counter to existing concepts regarding the incidence and clinical significance of locally recurrent prostate cancer. In modern radical prostatectomy series, the reported incidence of isolated local recurrence ranges from 6% to 19%.^{32,36,37} Because these studies defined local recurrence as abnormal digital rectal examination findings or a positive pros-

Figure 2. Four-Year Actuarial Progression-Free Probability (PFP) After Salvage Radiotherapy



Progression-free probability (PFP) stratified by Gleason score, preradiotherapy prostate-specific antigen (PSA) level, surgical margins, and PSA doubling time (PSADT). Patients receiving neoadjuvant androgen deprivation therapy (ADT) were excluded from this analysis. All values in parentheses are 95% confidence intervals. RT indicates radiotherapy.

tatic fossa biopsy result, the incidence of locally recurrent cancer was likely underappreciated and biased toward patients with higher-volume disease.^{10,38} Based on the 4-year PFP for patients receiving early salvage radiotherapy, 52% of patients with an increasing PSA level will have disease initially confined to the pelvis. The 67% complete response rate to salvage radiotherapy that we observed also suggests that residual pelvic disease initially accounts for the bulk of recurrent prostate cancer, even in patients with combined local and distant recurrence. As this estimate of local recurrence assumes that all patients with isolated local recurrence were cured by salvage radiotherapy, the true rate of isolated local recurrence may be considerably higher than 50%. This suggests that the incidence of isolated local recurrence after radical prostatectomy appears to be closer to the estimate of Lightner et al,³⁹ who reported a biopsy-proven local recurrence rate of 42% in patients with an increasing PSA level after radical prostatectomy.

Until now, it has been widely believed that locally recurrent prostate cancer is biologically different from metastatic disease and results from inadequate surgery rather than from inherent aggressive tumor biology. Partin et al⁶ proposed criteria to distinguish local recurrence from distant metastases for patients with an increasing PSA level after radical prostatectomy. A Gleason score of 8 to 10, seminal vesicle invasion, positive lymph nodes, and a rapid PSA velocity were associated with distant metastases. Local recurrence was more frequently observed in patients with low-grade and organ-confined disease, a slow PSA velocity, and a disease-free interval greater than 3 years, suggesting that isolated local recurrence has a low metastatic potential.²

In contrast to these beliefs, our study demonstrates that locally recurrent prostate cancer frequently has features that are often associated with the development of distant metastases if the disease is left untreated. Of the patients who were free of PSA progression for a mini-

mum of 4 years after salvage radiotherapy, 15% had Gleason scores of 8 to 10, 38% had a PSADT of 10 months or less, and 70% had a disease-free interval of 12 months or less after radical prostatectomy. In our study, the majority of patients with positive surgical margins and either a Gleason score of 8 to 10 or a rapid PSADT achieved a durable response to salvage radiotherapy. This evidence suggests the existence of a substantial number of patients with aggressive, recurrent prostate cancer initially confined to the pelvis that has not yet metastasized and that may be effectively treated with radiation therapy if it is delivered early in the course of recurrent disease.

This estimate of the incidence and disease characteristics of local recurrence assumes that the patients in our study are representative of all patients with postprostatectomy PSA recurrence. Our cohort is composed of selected patients whom clinicians believed would likely benefit from salvage radiotherapy and therefore may reflect a biased selection of this patient population. However, the clinical features of our cohort are similar to those of 2 studies examining predictors of clinical disease progression (in the absence of salvage ADT) in consecutive patients with recurrent disease after radical prostatectomy with respect to preoperative PSA level, Gleason score, pathological stage, disease-free interval after radical prostatectomy, and PSADT.^{2,3} The proportion of patients in our study with positive lymph nodes was similar to that in the study by Roberts et al³ but significantly lower than that in the study by Pound et al.²

The role of salvage radiotherapy in the treatment of patients with an increasing PSA level after radical prostatectomy remains controversial. No study has shown that salvage radiotherapy improves survival or prevents the development of distant metastases. However, our study demonstrates that salvage radiotherapy can interrupt the natural history of patients with PSA recurrence after radical prostatectomy, even for those patients at the highest risk of progres-

sion to distant metastases and death from prostate cancer. In general, salvage radiotherapy appears to be an underused treatment option for patients who experience relapse after radical prostatectomy. Based on our results, we believe that patients with positive surgical margins who experience relapse after radical prostatectomy should be strongly considered for salvage radiotherapy, even those with high-grade disease and/or a rapid PSADT. We have developed a predictive model to estimate the likelihood of treatment success for a given individual that will help guide physicians in the selection of patients for this therapy.⁴⁰

The clinical implications of our findings are that locally recurrent prostate cancer appears to be more common than previously reported, that it is frequently associated with aggressive features, and that salvage radiotherapy offers the possibility of cure for a substantial proportion of patients with a rapid PSADT and high-grade cancer. Ultimately, a randomized trial is needed to investigate whether, in an identifiable group of patients, salvage radiotherapy can prevent distant metastases and improve the survival of patients with recurrent prostate cancer after radical prostatectomy.

Author Affiliations: Department of Urology, Sidney Kimmel Center for Prostate and Urologic Cancers (Drs Stephenson, Kattan, and Scardino) and Departments of Radiation Oncology (Drs Zelefsky, Katz, and Leibel) and Epidemiology and Biostatistics (Dr Kattan), Memorial Sloan-Kettering Cancer Center, New York, NY; Departments of Urology (Drs Shariat and Roehrborn) and Radiation Oncology (Dr Pistenmaa), University of Texas-Southwestern Medical Center, Dallas; Departments of Urology (Dr Klein) and Radiation Oncology (Dr Kupelian), Cleveland Clinic, Cleveland, Ohio; Department of Radiation Oncology (Drs Pacholke and Liauw), University of Florida, Gainesville; Scott Department of Urology (Dr Slawin) and Department of Radiation Oncology (Drs Butler and Teh), Baylor College of Medicine and the Methodist Hospital, Houston, Tex.

Author Contributions: Dr Slawin, as principal investigator of this study, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.

Study concept and design: Stephenson, Shariat, Zelefsky, Kattan, Leibel, Scardino, Slawin.

Acquisition of data: Stephenson, Shariat, Zelefsky, Butler, Teh, Klein, Kupelian, Roehrborn, Pistenmaa, Pacholke, Liauw, Katz, Leibel, Slawin.

Analysis and interpretation of data: Stephenson, Shariat, Zelefsky, Kattan, Klein, Roehrborn, Scardino, Slawin.

Drafting of the manuscript: Stephenson, Teh, Klein, Roehrborn, Scardino, Slawin.

Critical revision of the manuscript for important intellectual content: Stephenson, Shariat, Zelefsky,

Kattan, Butler, Teh, Klein, Kupelian, Pistenmaa, Pacholke, Liauw, Katz, Leibel, Scardino, Slawin. *Statistical expertise:* Stephenson, Shariat, Kattan. *Obtained funding:* Shariat, Kattan, Scardino, Slawin. *Administrative, technical, or material support:* Stephenson, Shariat, Butler, Teh, Roehrborn, Pacholke, Liauw, Slawin. *Study supervision:* Stephenson, Shariat, Zelefsky, Kattan, Teh, Kupelian, Roehrborn, Leibel, Scardino, Slawin.

Funding/Support: This study was supported in part by funds from National Cancer Institute grant CA-92629 SPORE in prostate cancer and by gifts from the Leon Lowenstein Foundation and the Frost Foundation. Dr Stephenson is supported in part by the American Foundation for Urologic Disease and by National Institutes of Health grant T32 CA-82088. Dr Shariat is supported in part by the Austrian Program for Advanced Research and Technology.

Role of the Sponsors: The National Cancer Institute, the Leon Lowenstein Foundation, the Frost Foundation, the American Foundation for Urologic Disease, the National Institutes of Health, and the Austrian Program for Advanced Research and Technology did not participate in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

REFERENCES

- Moul JW. Prostate specific antigen only progression of prostate cancer. *J Urol.* 2000;163:1632-1642.
- Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA.* 1999;281:1591-1597.
- Roberts SG, Blute ML, Bergstralh EJ, Slezak JM, Zincke H. PSA doubling time as a predictor of clinical progression after biochemical failure following radical prostatectomy for prostate cancer. *Mayo Clin Proc.* 2001;76:576-581.
- Patel A, Dorey F, Franklin J, deKernion JB. Recurrence patterns after radical retropubic prostatectomy: clinical usefulness of prostate specific antigen doubling times and log slope prostate specific antigen. *J Urol.* 1997;158:1441-1445.
- Thomas CT, Bradshaw PT, Pollock BH, et al. Indium-111-capromab pendetide radioimmunoscintigraphy and prognosis for durable biochemical response to salvage radiation therapy in men after failed prostatectomy. *J Clin Oncol.* 2003;21:1715-1721.
- Partin AW, Pearson JD, Landis PK, et al. Evaluation of serum prostate-specific antigen velocity after radical prostatectomy to distinguish local recurrence from distant metastases. *Urology.* 1994;43:649-659.
- Cher ML, Bianco FJ Jr, Lam JS, et al. Limited role of radionuclide bone scintigraphy in patients with prostate specific antigen elevations after radical prostatectomy. *J Urol.* 1998;160:1387-1391.
- Zelefsky MJ, Fuks Z, Hunt M, et al. High-dose intensity modulated radiation therapy for prostate cancer: early toxicity and biochemical outcome in 772 patients. *Int J Radiat Oncol Biol Phys.* 2002;53:1111-1116.
- Shibley WU, Thames HD, Sandler HM, et al. Radiation therapy for clinically localized prostate cancer: a multi-institutional pooled analysis. *JAMA.* 1999;281:1598-1604.
- Leventis AK, Shariat SF, Kattan MW, Butler EB, Wheeler TM, Slawin KM. Prediction of response to salvage radiation therapy in patients with prostate cancer recurrence after radical prostatectomy. *J Clin Oncol.* 2001;19:1030-1039.
- Katz MS, Zelefsky MJ, Venkatraman ES, Fuks Z, Hummer A, Leibel SA. Predictors of biochemical outcome with salvage conformal radiotherapy after radical prostatectomy for prostate cancer. *J Clin Oncol.* 2003;21:483-489.
- Liauw SL, Webster WS, Pistenmaa DA, Roehrborn CG. Salvage radiotherapy for biochemical failure of radical prostatectomy: a single-institution experience. *Urology.* 2003;61:1204-1210.
- Song DY, Thompson TL, Ramakrishnan V, et al. Salvage radiotherapy for rising or persistent PSA after radical prostatectomy. *Urology.* 2002;60:281-287.
- Koppie TM, Grossfeld GD, Nudell DM, Weinberg VK, Carroll PR. Is anastomotic biopsy necessary before radiotherapy after radical prostatectomy? *J Urol.* 2001;166:111-115.
- Anscher MS, Clough R, Dodge R. Radiotherapy for a rising prostate-specific antigen after radical prostatectomy: the first 10 years. *Int J Radiat Oncol Biol Phys.* 2000;48:369-375.
- Pisansky TM, Kozelsky TF, Myers RP, et al. Radiotherapy for isolated serum prostate specific antigen elevation after prostatectomy for prostate cancer. *J Urol.* 2000;163:845-850.
- Ravery V, Lamotte F, Hennequin CH, et al. Adjuvant radiation therapy for recurrent PSA after radical prostatectomy in T1-T2 prostate cancer. *Prostate Cancer Prostatic Dis.* 1998;1:321-325.
- Rogers R, Grossfeld GD, Roach M III, Shinohara K, Presti JC Jr, Carroll PR. Radiation therapy for the management of biopsy proved local recurrence after radical prostatectomy. *J Urol.* 1998;160:1748-1753.
- Forman JD, Duclos M, Shamsa F, Pontes EJ. Predicting the need for adjuvant systemic therapy in patients receiving postprostatectomy irradiation. *Urology.* 1996;47:382-386.
- Wu JJ, King SC, Montana GS, McKinstry CA, Anscher MS. The efficacy of postprostatectomy radiotherapy in patients with an isolated elevation of serum prostate-specific antigen. *Int J Radiat Oncol Biol Phys.* 1995;32:317-323.
- Valicenti RK, Gomella LG, Ismail M, et al. Durable efficacy of early postoperative radiation therapy for high-risk pT3N0 prostate cancer: the importance of radiation dose. *Urology.* 1998;52:1034-1040.
- Eulau SM, Tate DJ, Stamey TA, Bagshaw MA, Hancock SL. Effect of combined transient androgen deprivation and irradiation following radical prostatectomy for prostatic cancer. *Int J Radiat Oncol Biol Phys.* 1998;41:735-740.
- Chawla AK, Thakral HK, Zietman AL, Shibley WU. Salvage radiotherapy after radical prostatectomy for prostate adenocarcinoma: analysis of efficacy and prognostic factors. *Urology.* 2002;59:726-731.
- Cadeddu JA, Partin AW, DeWeese TL, Walsh PC. Long-term results of radiation therapy for prostate cancer recurrence following radical prostatectomy. *J Urol.* 1998;159:173-177; discussion 177-178.
- Cox JD, Gallagher MJ, Hammond EH, Kaplan RS, Schellhammer PF, American Society for Therapeutic Radiology and Oncology Consensus Panel. Consensus statements on radiation therapy of prostate cancer: guidelines for prostate re-biopsy after radiation and for radiation therapy with rising prostate-specific antigen levels after radical prostatectomy. *J Clin Oncol.* 1999;17:1155-1163.
- Grossfeld GD, Stier DM, Flanders SC, et al. Use of second treatment following definitive local therapy for prostate cancer: data from the caPSURE database. *J Urol.* 1998;160:1398-1404.
- Ornstein DK, Colberg JW, Virgo KS, et al. Evaluation and management of men whose radical prostatectomies failed: results of an international survey. *Urology.* 1998;52:1047-1054.
- Amling CL, Bergstralh EJ, Blute ML, Slezak JM, Zincke H. Defining prostate specific antigen progression after radical prostatectomy: what is the most appropriate cut point? *J Urol.* 2001;165:1146-1151.
- Pruthi RS, Johnstone I, Tu IP, Stamey TA. Prostate-specific antigen doubling times in patients who have failed radical prostatectomy: correlation with histologic characteristics of the primary cancer. *Urology.* 1997;49:737-742.
- D'Amico AV, Cote K, Loffredo M, Renshaw AA, Schultz D. Determinants of prostate cancer-specific survival after radiation therapy for patients with clinically localized prostate cancer. *J Clin Oncol.* 2002;20:4567-4573.
- Hull GW, Rabbani F, Abbas F, Wheeler TM, Kattan MW, Scardino PT. Cancer control with radical prostatectomy alone in 1,000 consecutive patients. *J Urol.* 2002;167(2 pt 1):528-534.
- Han M, Partin AW, Pound CR, Epstein JI, Walsh PC. Long-term biochemical disease-free and cancer-specific survival following anatomic radical retropubic prostatectomy: the 15-year Johns Hopkins experience. *Urol Clin North Am.* 2001;28:555-565.
- Wieder JA, Soloway MS. Incidence, etiology, location, prevention and treatment of positive surgical margins after radical prostatectomy for prostate cancer. *J Urol.* 1998;160:299-315.
- Eastham JA, Kattan MW, Riedel E, et al. Variations among individual surgeons in the rate of positive surgical margins in radical prostatectomy specimens. *J Urol.* 2003;170(6 pt 1):2292-2295.
- Zelefsky MJ, Leibel SA, Gaudin PB, et al. Dose escalation with three-dimensional conformal radiation therapy affects the outcome in prostate cancer. *Int J Radiat Oncol Biol Phys.* 1998;41:491-500.
- Zincke H, Oesterling JE, Blute ML, Bergstralh EJ, Myers RP, Barrett DM. Long-term (15 years) results after radical prostatectomy for clinically localized (stage T2c or lower) prostate cancer. *J Urol.* 1994;152(5 pt 2):1850-1857.
- Holmberg L, Bill-Axelsson A, Helgesen F, et al. A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer. *N Engl J Med.* 2002;347:781-789.
- Leventis AK, Shariat SF, Slawin KM. Local recurrence after radical prostatectomy: correlation of US features with prostatic fossa biopsy findings. *Radiology.* 2001;219:432-439.
- Lightner DJ, Lange PH, Reddy PK, Moore L. Prostate specific antigen and local recurrence after radical prostatectomy. *J Urol.* 1990;144:921-926.
- Stephenson AJ, Shariat SF, Kattan MW, et al. Predicting the outcome of salvage radiotherapy for suspected local recurrence of prostate cancer after radical prostatectomy. *Proc Am Soc Clin Oncol.* 2003;22:1577A.