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Predicting the Outcome of Salvage Radiation Therapy for Recurrent Prostate Cancer After Radical Prostatectomy

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This nomogram has been adapted for use on personal digital assistants and personal computers and is available in the public domain for free download at http://www.nomograms.org.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Abstract

Purpose—An increasing serum prostate-specific antigen (PSA) level is the initial sign of recurrent prostate cancer among patients treated with radical prostatectomy. Salvage radiation therapy (SRT) may eradicate locally recurrent cancer, but studies to distinguish local from systemic recurrence lack adequate sensitivity and specificity. We developed a nomogram to predict the probability of cancer control at 6 years after SRT for PSA-defined recurrence.

Patients and Methods—Using multivariable Cox regression analysis, we constructed a model to predict the probability of disease progression after SRT in a multi-institutional cohort of 1,540 patients.

Results—The 6-year progression-free probability was 32% (95% CI, 28% to 35%) overall. Forty-eight percent (95% CI, 40% to 56%) of patients treated with SRT alone at PSA levels of 0.50 ng/mL or lower were disease free at 6 years, including 41% (95% CI, 31% to 51%) who also had a PSA doubling time of 10 months or less or poorly differentiated (Gleason grade 8 to 10) cancer. Significant variables in the model were PSA level before SRT ($P < .001$), prostatectomy Gleason grade ($P < .001$), PSA doubling time ($P < .001$), surgical margins ($P < .001$), androgen-deprivation therapy before or during SRT ($P < .001$), and lymph node metastasis ($P = .019$). The resultant nomogram was internally validated and had a concordance index of 0.69.

Conclusion—Nearly half of patients with recurrent prostate cancer after radical prostatectomy have a long-term PSA response to SRT when treatment is administered at the earliest sign of recurrence. The nomogram we developed predicts the outcome of SRT and should prove valuable for medical decision making for patients with a rising PSA level.

INTRODUCTION

An estimated 25% of patients treated with radical prostatectomy (RP) for clinically localized prostate cancer will suffer recurrence of their disease, manifested initially as a rising serum prostate-specific antigen (PSA) level with no radiographic evidence of cancer.[1] In the absence of salvage therapy, the median time from PSA recurrence to distant metastasis is 8 years.[2]

A critical issue in the management of these patients is determining whether a rising PSA reflects local or distant recurrence, as the former may potentially be cured by salvage radiation therapy (SRT). Androgen-deprivation therapy (ADT) appears only to offer palliation for those patients with recurrent prostate cancer. For the best chance of success, SRT to the local tumor bed must be administered when the cancer burden is lowest; that is, when the serum PSA first reaches detectable levels.[3–15] At these PSA levels, neither imaging studies nor anastomotic biopsy are sufficiently sensitive or specific enough to distinguish those with local recurrence who are suitable for SRT from those with disseminated disease who require systemic therapy.[16–19] As a consequence, the reported success rate of SRT after RP has been poor, ranging from 10% to 40%.[4,7,8,12,13,15,20,21]

PSA recurrence associated with a rapidly rising PSA (quantified by a short PSA doubling time [PSADT]), poorly differentiated cancer (Gleason grade 8 to 10), and a short disease-free interval after RP identifies patients at the highest risk for progression to distant metastasis and cancer-specific mortality who are in the greatest need of effective salvage therapy.[2,22,23] PSA recurrence associated with these features is widely believed to represent occult metastatic disease. Hence, most high-risk patients with a rising PSA are treated with early ADT despite the lack of conclusive evidence that that it prolongs survival,[24] and the potential for long-term

toxicity and adverse effects on quality of life.[25,26] However, a recent retrospective study demonstrated that a substantial proportion of recurrent patients with a short PSADT and/or Gleason grade 8 to 10 cancer were cancer free at 4 years after SRT alone,[13] but this favorable outcome was dependent on several disease parameters.

Because of the inadequacies of current diagnostic modalities for selecting patients for SRT and the variable outcome depending on patient parameters, models that accurately predict the outcome of SRT on the basis of the overall characteristics of an individual's case rather than a single parameter (eg, PSADT) are needed to select patients for this therapy. We present a predictive model called a nomogram that predicts the 6-year progression-free probability after SRT for men with PSA recurrence after RP.

PATIENTS AND METHODS

For the purpose of developing predictive models for the outcome of SRT, a multi-institutional, retrospective cohort of 1,603 consecutive patients from 17 North American tertiary referral centers who received SRT after RP for PSA recurrence between 1987 and 2005 was assembled. Before SRT, all patients had a PSA level of 0.2 ng/mL or higher at least 6 weeks after RP followed by another higher value, or a single PSA of 0.5 ng/mL or higher.[27] Sixty-three patients (4%) received adjuvant ADT after SRT and were excluded from the analysis of PSA-defined end points, leaving 1,540 patients for nomogram development and validation (Table 1). With the exception of a higher positive surgical margin rate and lower rates of seminal vesicle invasion and lymph node metastasis, the clinical characteristics of this cohort were similar to those of consecutive patients with PSA recurrence in RP series.[2,28]

Because some patients underwent RP at an outside institution, the method by which the pathologic specimens were processed was not available for all patients. PSADT was calculated using previously described methods based on a minimum of two PSA values at least 6 weeks apart.[2] Two hundred fourteen patients (14%) received ADT before and/or during SRT for a median duration of 4.1 month (range, 1 to 24 months); 25% of these patients received ADT for longer than 6 months.

After radiation treatment, patients were followed with clinical assessment and serum PSA determinations at regular intervals. The use of diagnostic imaging studies and salvage ADT was not standardized, and varied over time and by individual physician practice. The median follow-up after the completion of SRT was 53 months (interquartile range, 28 to 81 months).

The primary end point of this study was disease progression after SRT, defined as a serum PSA value of 0.2 ng/mL or more above the postradiotherapy nadir followed by another higher value, a continued rise in the serum PSA despite SRT, initiation of systemic therapy after completion of SRT, or clinical progression. Progression-free probability was estimated using the Kaplan-Meier method, and survival was calculated from the completion date of radiotherapy with no back-dating of recurrence. Multivariable Cox proportional hazards regression analysis was the basis for the nomogram. Variables to be used in the nomogram were selected on the basis of knowledge of their prognostic significance from previous reports. All decisions with respect to the categorization of variables were made before modeling. Because of skewed distributions, continuous variables were modeled using restricted cubic splines to accommodate potentially nonlinear effects.

Internal validation of the nomogram was performed using two components. First, a concordance index (*c*-index), which is similar to an area under the receiver operating characteristic curve, was estimated by subjecting the nomogram to bootstrapping with 200 resamples to calculate an unbiased measure of its ability to discriminate among patients.[29,30] The *c*-index is the probability that, given two randomly drawn patients, the patient who

relapses first had a higher probability of recurrence. With this measure, a *c*-index of 1.0 represents a perfectly discriminating model, and a value of 0.5 is that expected by random chance. The second component of validation compared the predicted probability of disease recurrence versus actual recurrence (ie, nomogram calibration) of the 1,540 patients using 200 bootstrap resamples to reduce overfit bias, which would overstate the accuracy of the nomogram.

All statistical analyses were conducted using *S*-Plus 2000 Professional statistical software (Insightful Corp, Seattle, WA) with the Design library attached.[31] All *P* values resulted from the use of two-sided statistical tests, and the level of significance was set at .05. The study was conducted under Health Insurance Portability and Accountability Act guidelines and received institutional review board approval from all participating institutions.

RESULTS

Overall, 866 patients experienced disease progression after SRT, and the 6-year progression-free probability was 32% (95% CI, 28% to 35%; Fig 1A). However, an estimated 48% (95% CI, 40% to 56%) who received SRT alone without ADT when the PSA was 0.50 ng/mL or less were disease free at 6 years compared with 40% (95% CI, 34% to 46%), 28% (95% CI, 20% to 35%), and 18% (95%, 14% to 22%) of those treated at PSA levels of 0.51 to 1.00, 1.01 to 1.50, and greater than 1.50 ng/mL, respectively (Fig 1B). The 6-year response to SRT among patients treated at PSA levels of 0.50 ng/mL or less appears to be durable because only two progression events were observed after 6 years among 32 patients at risk at 6 years (median follow-up, 90 months).

Sufficient data to evaluate the PSA response to SRT was available for 1,491 patients (97%). A PSA nadir after radiotherapy of 0.10 ng/mL or less was achieved in 905 patients (59%), including 726 (55%) of 1,326 patients who did not receive ADT.

We previously reported favorable 4-year response rates after SRT alone in 356 patients with a short PSADT and Gleason grade 8 to 10 cancer.[13] In this larger cohort with longer follow-up, the 4-year progression-free probability estimates after SRT alone stratified by PSA before SRT (cut point, 2.0 ng/mL), Gleason grade 7 or less surgical versus 8 to 10, surgical margins, and PSADT (cut point, 10 months) were generally within 10% of those previously reported, validating the favorable intermediate prognosis in select high-risk patients (Fig 2). When SRT was administered at PSA levels of 0.50 ng/mL or less, an estimated 41% (95% CI, 31% to 51%) of patients with a PSADT of 10 months or less or Gleason grade 8 to 10 cancer were disease free at 6 years, including 48% (95% CI, 35% to 62%) who also had positive surgical margins.

A nomogram predicting the 6-year progression-free probability after SRT was constructed from 11 parameters determined before treatment (Fig 3A). Statistically significant variables in the model were PSA level before SRT ($P < .001$), prostatectomy Gleason grade ($P < .001$), PSADT ($P < .001$), surgical margins ($P < .001$), ADT administered before or during SRT ($P < .001$), and lymph node metastasis ($P = .019$). Statistically insignificant variables were not omitted from the model because of the resultant bias on the remaining predictors and subsequent deleterious effect on predictive accuracy. The predictive accuracy as measured by the *c*-index was 0.69 in internal validation. The nomogram was well calibrated, and there was good correlation between predicted and observed outcome across the spectrum of predictions (Fig 3B).

The ability of the nomogram to discriminate among patients for the outcome of SRT was compared with published models (based on PSADT, disease-free interval, and/or Gleason grade) developed to predict the probability of metastases[2] and of cancer-specific

mortality[22,23] for patients with a rising PSA after RP (Table 2). The predictive accuracy of these models was marginally better than that expected by chance (*c*-index, 0.56 to 0.60) in our cohort, and substantially inferior to the nomogram. The *c*-index of PSA before SRT as a single parameter was 0.61.

DISCUSSION

Patients with a rising PSA after RP have a 60% probability of developing distant metastasis and a 20% probability of dying as a result of prostate cancer within 10 years.[1,2] For those with poorly differentiated cancer and a short PSADT, the median metastasis-free and cancer-specific survival is 3 and 5 years, respectively.[2,23] A critical issue in the management of these patients is determining whether a rising PSA results from local or distant recurrence, because the former may potentially be cured with SRT. Up to 50% of patients with PSA recurrence may initially have local or regional disease, and thereby benefit from SRT,[28] but current diagnostic modalities have proven inadequate for selecting patients. To address this issue, we developed a nomogram to predict the 6-year progression-free probability after SRT. Nomograms predicting the outcome of definitive local therapy for prostate cancer are the most widely used disease-specific prediction tools in oncology.[32–35] This nomogram is the first model to predict the outcome of salvage therapy for a rising PSA after RP and is anticipated to be useful for medical decision making.

The PSA level before SRT was a highly significant predictor of disease progression, with more favorable outcomes observed at low PSA levels. An estimated 48% of patients who received SRT alone at PSA levels of 0.50 ng/mL or less were free of progression at 6 years, compared with 26% for those treated at higher PSA levels. The ability to provide successful salvage treatment for approximately 50% of patients with “early” SRT is similar to the 52% to 57% relative risk reduction in the rate of PSA progression among high-risk patients randomly assigned to adjuvant radiotherapy versus observation after RP in two recent randomized trials.[36,37] An important observation in our study is that the 6-year responses for those treated at PSA levels less than 0.50 ng/mL appeared to be durable. This evidence suggests that approximately 50% of patients with recurrent prostate cancer after RP may derive long-term benefit from SRT when it is administered at the earliest signs of recurrence.

The favorable outcome associated with SRT at lower PSA levels suggests that intervention when the cancer burden is lowest and most amenable to therapy, and before systemic dissemination, leads to improved outcome. Alternatively, this favorable result may be explained by the indolent natural history of PSA recurrence in some patients with a single PSA elevation between 0.2 and 0.39 ng/mL.[27,38] However, we included in our analysis only patients who experienced two or more PSA rises at levels of 0.2 ng/mL or higher or a single PSA level of 0.5 ng/mL or higher, which are associated with a risk of subsequent PSA progression that is greater than 90%.[27] The PSA level before SRT was also a highly significant predictor of progression in our multivariable analysis after controlling for all other important parameters.

SRT is most frequently recommended to patients judged to be at low-risk for occult metastases,[39] because cancer control rates in such patients range up to 77%.[13] Our study demonstrates that select patients with a short PSADT or Gleason grade 8 to 10 cancer may also benefit from SRT, validating previously published results.[13] The 41% disease-free estimate at 6 years in patients with a PSADT of 10 months or less or Gleason grade 8 to 10 cancer treated at low PSA levels is potentially clinically significant considering that these patients have a 60% to 70% probability of developing metastatic disease within the same time period in the absence of salvage therapy.[2] This suggests that SRT may prevent or delay the appearance of metastatic disease in a substantial proportion of patients.

The potential for morbidity resulting from radiation therapy argues against its indiscriminate use in the salvage setting. Mild to moderate acute rectal and genitourinary toxicity is seen in the majority of patients, but the reported incidence of acute grade 3 to 4 complications is less than 4%.[4,6,9,14,21,36] Late grade 1 to 2 rectal and genitourinary toxicity are reported in 5% to 20% of patients, and late grade 3 toxicity is less than 4%.[3,4,6,8,11,21] Although rare, pelvic radiation therapy for prostate cancer is associated with an increased risk of secondary pelvic malignancies.[40] Postprostatectomy radiotherapy does not appear to significantly increase the risk of urinary incontinence,[3,4,6,14,21,41] but we must presume that it has some adverse effect on erectile function on the basis of the data from primary radiation therapy series. The nomogram can be used to restrict SRT to those patients most likely to benefit and avoid treatment-related morbidity in those predicted to have a low probability of a long-term benefit.

The present study has several limitations worth noting. The *c*-index of the model (0.69) indicates that its predictive accuracy is slightly worse than midway between a perfect model (1.0) and a coin flip (0.5); previous prostate cancer nomograms for RP and external-beam radiotherapy had *c*-indices near 0.75.[32,33,42,43] As a retrospective, multi-institutional cohort of patients whose disease was managed over an 18-year time period, this may be attributable to variations among institutions (and over time) in pathologic staging, clinical staging before SRT, radiation therapy techniques and the use and duration of ADT, and surveillance protocols regarding the frequency of PSA testing. Despite this limitation, we believe that the nomogram performs better than any other model or imaging modality for predicting the outcome of SRT.

Another limitation of the model is the fact that it predicts the probability of being free of recurrence at 6 years, and some patients may still experience progressive disease more than 6 years after SRT. The nomogram also does not provide information on the probability of developing metastatic disease or dying as a result of prostate cancer after SRT. The favorable 6-year biochemical disease-free rates observed among patients with a short PSADT and/or poorly differentiated cancer who received SRT at low PSA levels suggests it may delay or prevent the emergence of metastatic disease, but we do not know how these patients would have fared without local salvage treatment. A randomized clinical trial is needed to determine whether SRT prevents clinical progression or improves the survival of patients with a rising PSA after RP. A randomized trial of adjuvant radiotherapy versus observation after RP for pathologic stage T3 prostate cancer showed a 25% relative risk reduction in the rate of distant metastasis at 10 years, but this result was not statistically significant.[37]

Recently, risk groups predicting the development of metastatic disease and cancer-specific mortality have been developed for the post-RP PSA recurrence population.[2,22,23] These tools are most helpful to estimate the risk a rising PSA poses to a man's longevity, but they do not provide information about which treatment should be considered. Physicians may be influenced by these tools to select patients for SRT despite the fact that they were not designed to identify local versus distant disease or the characteristics of patients who will respond favorably to SRT. The nomogram was substantially better at predicting the outcome of SRT than were these models, which performed marginally better than that expected by random chance.

A rising PSA alone is not justification for initiating salvage therapy because patients with PSA recurrence are as likely to die as a result of competing causes as they are of prostate cancer.[1] To determine the need for salvage therapy, we suggest using one of several existing tools to estimate the probability of developing metastatic disease or cancer-specific mortality.[2,22,23] Patients at high risk of progression to these clinically significant events and/or a long life expectancy should be assessed for SRT using our nomogram. We have avoided specifying a minimum prediction at which SRT should not be considered. We believe this decision should be made after a discussion between the patient and his physician focusing on the probabilities

of treatment success, toxicity, and the risk of clinical disease progression if observation is chosen. Therapeutic options for patients with a low probability of a durable response to SRT include immediate or deferred ADT or entry onto clinical trials.

In the setting of primary radiotherapy, dose escalation and combined therapy with ADT have been proven to increase local control, disease-free survival, and/or overall survival.[44–46] No prospective study has evaluated the impact of ADT in the salvage setting. ADT administered before and/or during SRT was associated with improved PSA control in our study, although this may potentially be explained by the effects of prolonged ADT (up to 24 months in some patients) on masking PSA recurrence. ADT may improve the efficacy of SRT, but a randomized trial is required to test this hypothesis. We did not identify an association between radiation dose and the outcome of SRT, although the range of doses administered was relatively narrow, and few patients received doses greater than 70 Gy. Combined therapy with ADT, radiation dose escalation, and improved target localization using modalities such as endorectal coil magnetic resonance imaging may improve the efficacy of SRT.[47]

In summary, the outcome of SRT is influenced by several disease-and treatment-related parameters and provides long-term control of disease in approximately one third of patients with PSA recurrence after RP. Improved results are observed when SRT is administered at low PSA levels, and a substantial proportion of patients with poorly differentiated cancer and a short PSADT are observed to benefit. The nomogram represents the best tool available to predict the outcome of SRT and is anticipated to be useful for medical decision making for patients with a rising PSA.

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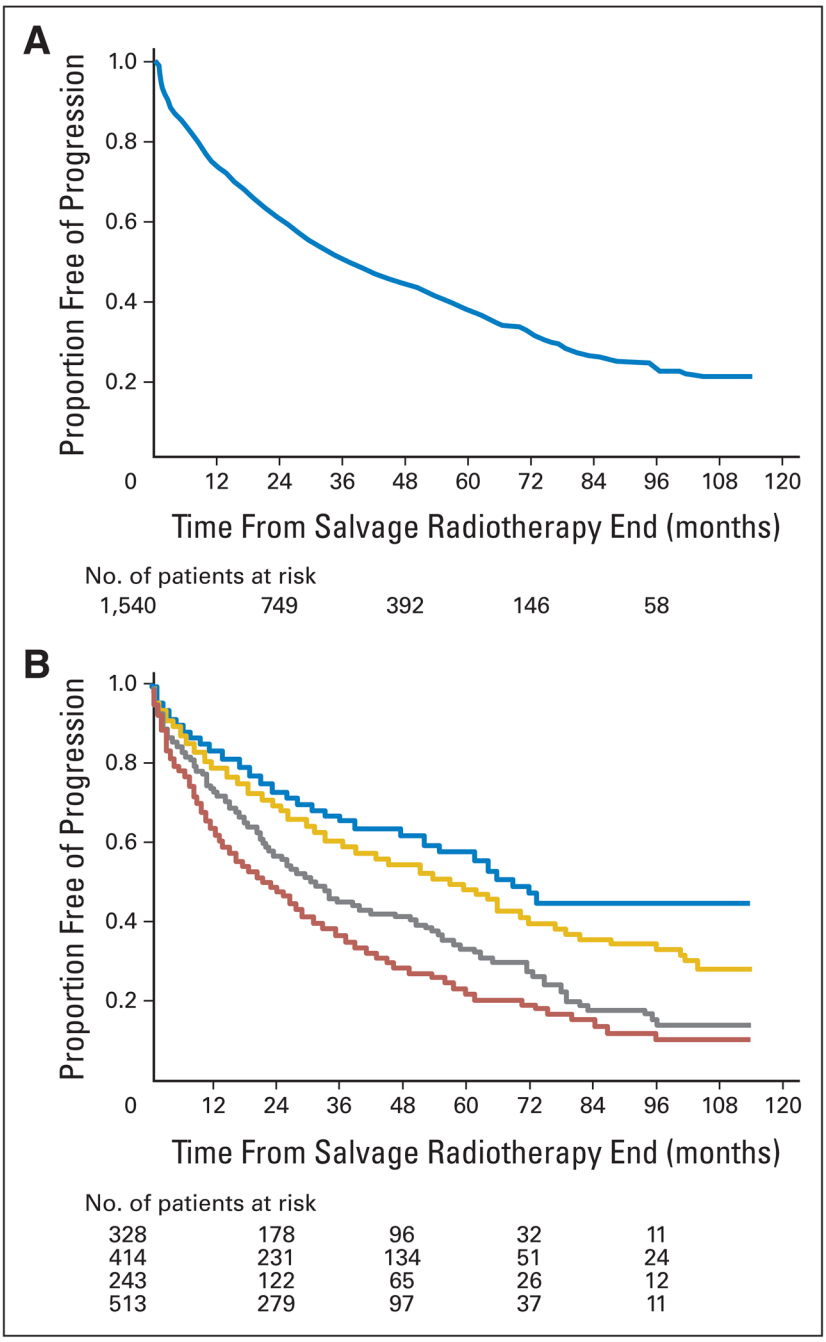

Fig 1.

(A) Kaplan-Meier estimate of the overall progression-free probability after salvage radiotherapy. (B) Progression-free probability after salvage radiotherapy stratified by preradiotherapy prostate-specific antigen 0.50 or less (blue), 0.51 to 1.00 (yellow), 1.01 to 1.50 (gray), and more than 1.50 ng/mL (red).

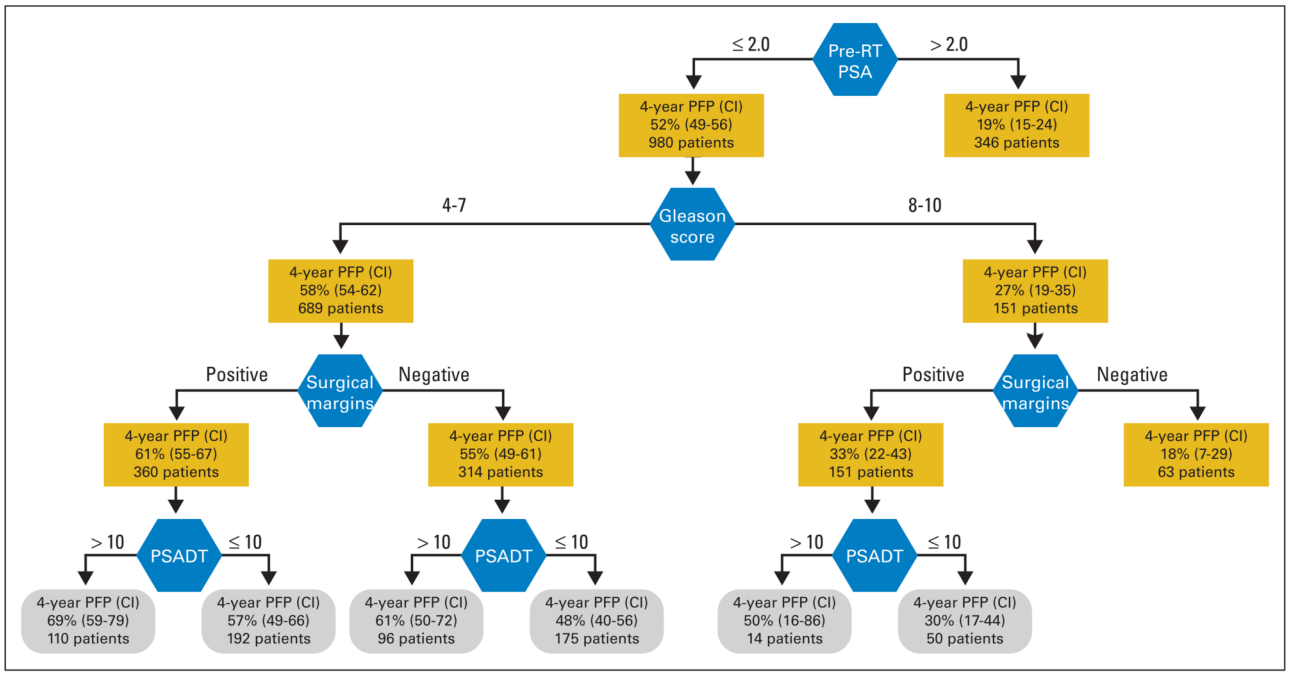

Fig 2.

Four-year progression-free probability after salvage radiotherapy for 1,326 patients who did not receive androgen-deprivation therapy before or during radiation therapy, stratified by preradiotherapy prostate-specific antigen (PSA), Gleason score, surgical margins, and PSA doubling time (PSADT). RT, radiotherapy; PFP, progression-free probability; CI, 95% CI.

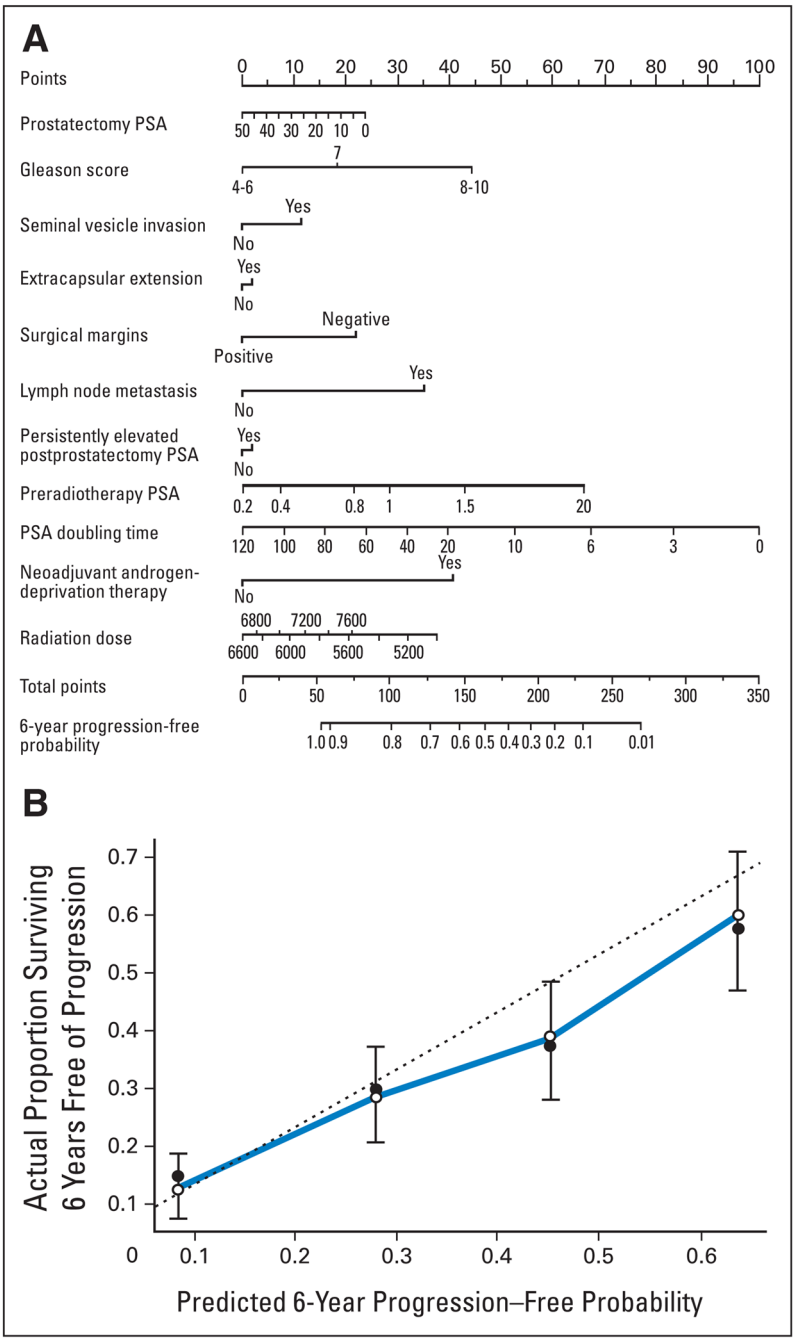

Fig 3.

(A) Pretreatment nomogram predicting 6-year progression-free probability after salvage radiotherapy for prostate-specific antigen (PSA) recurrence after radical prostatectomy. (B) Calibration of the nomogram. Dashed line indicates reference line where an ideal nomogram would lie. Solid line indicates the performance of the current nomogram. Dots are quartiles of our data set. Instructions: Locate the patient's Gleason score on the respective axis. Draw a straight line up to the Points axis to determine how many points toward disease recurrence that the patient receives for his or her Gleason score. Repeat this process for the other 10 disease and treatment parameters. Sum the points and locate this number on the Total Points axis. Draw

a straight line down to find the patient's probability of remaining free of disease progression at 6 years after salvage radiotherapy, provided the patient does not die of another cause first.

Table 1

Clinical Characteristics of 1,540 Patients Undergoing Salvage Radiotherapy for PSA Recurrence After Radical Prostatectomy.

Parameter	No.	%	IQR
Median preprostatectomy age, years	62		58 to 67
Median preprostatectomy PSA, ng/mL	10.5		6.6 to 19
Prostatectomy Gleason grade			
4–6	351	26	
7	687	52	
8–10	293	22	
Extracapsular extension	996	65	
Positive surgical margins	787	51	
Seminal vesicle invasion	371	24	
Positive lymph nodes	48	3	
Median disease-free interval, months	15		5.1 to 34.0
Persistently elevated postprostatectomy PSA, %	449	29	
Median PSA level before radiotherapy, ng/mL	1.1		0.6 to 2.2
Median PSA doubling time, months	6.9		3.6 to 12.2
Preradiotherapy ADT	214	14	
Median radiotherapy dose, Gy	64.8		63 to 66
Median follow-up after prostatectomy, months	90		61 to 120
Median follow-up after PSA recurrence, months	64		38 to 95
Median follow-up after radiotherapy, months	53		28 to 81

Abbreviations: PSA, prostate-specific antigen; IQR, interquartile range; ADT, androgen-deprivation therapy.

Table 2

Comparison of the Predictive Accuracy of Various Risk Stratification Models for the Rising PSA State for the Outcome of Salvage Radiotherapy

Model	End Point	*c*-Index
Nomogram	6-year PFP after salvage radiotherapy	0.69*
PSA doubling time		0.60
Freedland et al 2005[23]	10-year cancer-specific survival after PSAR	0.59
Pound et al 1999[2]	7-year metastasis-free probability after PSAR	0.56

*Concordance index derived from bootstrap internal validation.

Abbreviations: PSA, prostate-specific antigen; *c*-index, concordance index; PFP, progression-free probability; PSAR, postprostatectomy PSA recurrence.