VOLUME 34 · NUMBER 30 · OCTOBER 20, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Contemporary Update of a Multi-Institutional Predictive Nomogram for Salvage Radiotherapy After Radical Prostatectomy

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Published online ahead of print at www.jco.org on August 15, 2016.

Presented in part at the 2015 Annual Meeting of the American Society for Radiation Oncology, San Antonio, TX, October 18-21, 2015.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

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0732-183X/16/3430w-3648w/$20.00

DOI: 10.1200/JCO.2016.67.9647

ABSTRACT

Purpose

We aimed to update a previously published, multi-institutional nomogram of outcomes for salvage radiotherapy (SRT) following radical prostatectomy (RP) for prostate cancer, including patients treated in the contemporary era.

Methods

Individual data from node-negative patients with a detectable post-RP prostate-specific antigen (PSA) treated with SRT with or without concurrent androgen-deprivation therapy (ADT) were obtained from 10 academic institutions. Freedom from biochemical failure (FFBF) and distant metastases (DM) rates were estimated, and predictive nomograms were generated.

Results

Overall, 2,460 patients with a median follow-up of 5 years were included; 599 patients (24%) had a Gleason score (GS) ≤ 6, 1,387 (56%) had a GS of 7, 244 (10%) had a GS of 8, and 230 (9%) had a GS of 9 to 10. There were 1,370 patients (56%) with extraprostatic extension (EPE), 452 (18%) with seminal vesicle invasion (SVI), 1,434 (58%) with positive surgical margins, and 390 (16%) who received ADT (median, 6 months). The median pre-SRT PSA was 0.5 ng/mL (interquartile range, 0.3 to 1.1). The 5-yr FFBF rate was 56% overall, 71% for those with a pre-SRT PSA level of 0.01 to 0.2 ng/mL (n = 441), 63% for those with a PSA of 0.21 to 0.50 ng/mL (n = 822), 54% for those with a PSA of 0.51 to 1.0 ng/mL (n = 533), 43% for those with a PSA of 1.01 to 2.0 ng/mL (n = 341), and 37% for those with a PSA > 2.0 ng/mL (n = 323); $P < .001$. On multivariable analysis, pre-SRT PSA, GS, EPE, SVI, surgical margins, ADT use, and SRT dose were associated with FFBF. Pre-SRT PSA, GS, SVI, surgical margins, and ADT use were associated with DM, whereas EPE and SRT dose were not. The nomogram concordance indices were 0.68 (FFBF) and 0.74 (DM).

Conclusion

Early SRT at low PSA levels after RP is associated with improved FFBF and DM rates. Contemporary nomograms can estimate individual patient outcomes after SRT in the modern era.

J Clin Oncol 34:3648-3654. © 2016 by American Society of Clinical Oncology

INTRODUCTION

More than half of men with adverse pathologic features will experience biochemical failure (BF), defined by a rise in serum prostate-specific antigen (PSA) level, after radical prostatectomy (RP) for clinically localized prostate cancer.[1-3] Postoperative salvage radiotherapy (SRT) to the prostate bed is a potentially curative option for many patients.[4] In 2007, Stephenson et al[5] published a nomogram to estimate biochemical outcomes following postprostatectomy SRT that has been widely used to predict the likelihood of success of salvage therapy. All patients included in that multi-institutional series were treated at a PSA level > 0.2 ng/mL. Since publication of this series, three randomized trials of adjuvant radiotherapy versus observation after RP have demonstrated a clinical benefit to early radiotherapy in patients with positive surgical margins, extraprostatic extension (EPE), and/or seminal vesicle invasion

(SVI).[1-3] Recently, the American Society for Radiation Oncology and American Urological Association (AUA) jointly published a consensus paper stating that postoperative radiotherapy "should be administered at the earliest sign of PSA recurrence," although an absolute PSA threshold was not identified.[6(p826)]

Early SRT has been advocated in select high-risk patients with any detectable postoperative PSA level, even if the AUA definition of BF has not yet been reached, an occurrence more frequent with the advent of ultrasensitive PSA assays.[7-10] However, predictive models of modern outcomes of early SRT in the context of ultrasensitive PSA assays are not widely available. The purpose of this investigation was to evaluate the benefit of SRT delivered at early PSA time points and to provide a contemporary update of the original Stephenson predictive nomogram for the end points of freedom from BF (FFBF) and distant metastases (DM), including patients treated with early SRT (at a PSA $\leq$ 0.2 ng/mL) who were not included in the original nomogram.

METHODS

Ten participating academic medical centers in the United States submitted data for analysis and nomogram construction. The study was conducted in accordance with Health Insurance Portability and Accountability Act guidelines and received institutional review board approval from all participating institutions.

All patients underwent open or laparoscopic RP and were subsequently treated with SRT for a detectable PSA on the basis of the assay used at the treating institution at that time. Patients were excluded if the PSA was undetectable at the time of RT delivery (ie, adjuvant RT); androgen-deprivation therapy (ADT) was initiated either before RP or more than 6 months before SRT; lymph nodes were histologically positive; and pathologic staging or follow-up details regarding the presence or absence of BF, DM, and vital status were unavailable. All patients were within a consecutive cohort of eligible patients treated at each institution. Overall, 2,460 patients treated with SRT between 1987 and 2013 met the inclusion criteria and were included in this analysis.

All patients were treated at high-volume, tertiary referral centers by physicians specializing in the care of genitourinary cancers. All clinical management decisions were at the discretion of the treating physicians. Patients underwent follow-up assessments with serum PSA testing at regular intervals on the basis of institutional clinical practice. Because of the retrospective nature of this study, there was no central pathology review and no uniform method of staging work-up. SRT treatment parameters and the use of ADT were by treating physician preference and on the basis of standards of care at the time of treatment.

BF after SRT was defined as serum PSA rising above the post-treatment nadir to a level of 0.2 ng/mL or more with a confirmatory value or by the initiation of salvage ADT after completion of SRT. The rates of BF and DM from the SRT end date were estimated by the cumulative incidence method of Fine and Gray,[11] to account for nonprostate cancer death as a competing risk.[12] Univariable analyses for the end points of BF and DM were performed by Fine and Gray's K-sample test for comparing the cumulative incidence of competing risks, and multivariable analyses were performed by competing risk regression.

Nomograms for the end points of FFBF and DM were generated from multivariable competing risk regression and validated internally with a 10-fold cross-validation method. Variables included in the nomogram were selected on the basis of their known prognostic significance from previous studies.[5] Results by tumor grade were analyzed by prostatectomy Gleason score (GS) recorded at the treating institution. A GS of 6 or less corresponds to the 2014 International Society of Urological Pathology grade group 1, a GS of 7 corresponds to grade group 2 to 3, a GS of 8 corresponds to grade group 4, and a GS of 9 to 10 corresponds to grade group 5.[13] Only the total GS was available for all patients; therefore, GS 7 patients were not subdivided into primary pattern 3 versus 4, nor were tertiary patterns factored into the analyses.

Notably, PSA doubling time (PSADT) was not considered in this model because of the inclusion of patients treated with early SRT at detectable PSA levels $<$ 0.2 ng/mL, in whom PSADT could not be accurately estimated. In addition, preoperative PSA and the presence of a persistently elevated post-RP PSA were omitted in this analysis because of their limited discriminatory value in the original nomogram. Pre-SRT PSA was modeled linearly up to 2 ng/mL determined on the basis of the results of the original nomogram. Lastly, the original nomogram demonstrated a nonlinear relationship between SRT dose and progression-free probability.[5] Thus, for this analysis, SRT dose was evaluated as a binary variable ($<$ 66 Gy $v \geq$ 66 Gy) rather than a continuous variable because of a subset analysis, which is the subject of a separate investigation and which is supported by the existing literature.[14,15] All statistical analyses were conducted using R software (version 3.1.1, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The baseline patient and treatment characteristics are listed in Table 1. There were 2,460 patients who met the criteria for inclusion, with a median follow-up of 5.0 years from the SRT end date. The median year of RP was 2000 (range, 1975 to 2012), and the median year of SRT was 2003 (range, 1987 to 2013). Overall, 599 patients (24%) had a GS $\leq$ 6; 1,387 (56%) had a GS of 7; 244 (10%) had a GS of 8; and 230 (9%) had a GS of 9 to 10. There were 1,370 (56%) with EPE; 452 (18%) with SVI; 1,434 (58%) with positive surgical margins; and 390 (16%) who received

Table 1. Patient and Treatment Characteristics

Characteristic	No. or Median (IQR)	%
Median (IQR) age at surgery, years	61 (56-66)	
Median (IQR) age at SRT, years	64 (59-70)	
Median (IQR) months from RP to SRT	25 (9-51)	
Gleason score (grade group)		
$\leq$ 6 (1)	599	24
7 (2-3)	1,387	56
8 (4)	244	10
9-10 (5)	230	9
Median (IQR) pre-SRT PSA, ng/mL	0.5 (0.3-1.1)	
0.01-0.2	441	18
0.21-0.5	822	33
0.51-1.0	533	22
1.01-2.0	341	14
$>$ 2.0	323	13
Extraprostatic extension	1,370	56
Seminal vesicle invasion	452	18
Surgical margins		
Positive	1,434	58
Negative	985	40
Unknown	41	2
Androgen-deprivation therapy	390	16
Median (IQR) radiation dose, Gy	66 (64.8-68.4)	
$<$ 66	1,164	47
$\geq$ 66	1,296	53
Radiation fields		
Prostate bed only	2,052	83
Pelvic nodal radiation	408	17

Abbreviations: IQR, interquartile range; PSA, prostate-specific antigen; RP, radical prostatectomy; SRT, salvage radiotherapy.

neoadjuvant/concurrent ADT for a median duration of 6 months (interquartile range [IQR], 5 to 24 months). The median pre-SRT PSA was 0.5 ng/mL (IQR, 0.3 to 1.1), and 441 patients (18%) received early SRT for a detectable PSA between 0.01 and 0.20 ng/mL, only 26 of whom were treated at a PSA level of ≤ 0.05 ng/mL. The median SRT dose to the prostate bed was 66 Gy (IQR, 64.8 to 68.4). Pelvic nodal radiation was given to 408 patients (17%). The median time from RP to initiation of SRT was 25 months (IQR, 9 to 51).

Figure 1 demonstrates the estimated rates of FFBF (Fig 1A) and DM (Fig 1B) according to pre-SRT PSA level. The 5-year rate of FFBF was 56% for all patients. The FFBF rate decreased with increasing PSA level: 71% for those with a pre-SRT PSA of 0.01 to 0.2 ng/mL (n = 441), 63% for a PSA of 0.21 to 0.50 ng/mL (n = 822), 54% for a PSA of 0.51 to 1.0 ng/mL (n = 533), 43% for a PSA of 1.01 to 2.0 ng/mL (n = 341), and 37% for a PSA > 2.0 ng/mL (n = 323); $P < .001$. The 10-year cumulative incidence rate of DM was 19% for all patients. Likewise, the DM rate increased with PSA level: 9% for those with a pre-SRT PSA of 0.01 to 0.2 ng/mL, 15% for a PSA of 0.21 to 0.50 ng/mL, 19% for a PSA of 0.51 to 1.0 ng/mL, 20% for a PSA of 1.01 to 2.0 ng/mL, and 37% for a PSA > 2.0 ng/mL; $P < .001$. The rates of FFBF and DM for subsets stratified by GS and pre-SRT PSA are listed in Table 2. For each GS subgroup, the rates of FFBF and DM were significantly associated with pre-SRT PSA.

Univariable and multivariable analyses for BF and DM were performed (Table 3). Higher pre-SRT PSA, higher GS, presence of EPE, SVI, negative surgical margins, lack of ADT, and lower SRT dose were significantly associated with increased BF ($P < .05$ for each). Higher pre-SRT PSA, higher GS, SVI, negative surgical margins, and lack of ADT were significantly associated with increased risk of DM ($P < .05$ for each). EPE and SRT dose were not associated with DM. Figures 2 and 3 depict the predictive nomograms and calibration plots for the outcomes of FFBF (concordance index, 0.68) and DM (concordance index, 0.74), respectively.

DISCUSSION

To our knowledge, this represents the largest multi-institutional case series of SRT outcomes in the literature to date. This update of a widely used predictive nomogram was developed to provide more contemporary individualized estimates of BF after SRT, including many patients treated in the modern era of ultrasensitive PSA assays. To our knowledge, it is the first investigation of its kind to estimate the risk of DM rates after SRT. In this study, we found that early SRT at the lowest detectable PSA is associated with improved FFBF and DM outcomes compared with SRT at higher PSA levels. Importantly, the absolute PSA level at which SRT is initiated is a potentially modifiable prognostic factor, and early initiation of SRT may help to reduce the risk of biochemical and metastatic disease progression.

The optimal postoperative management of men with prostate cancer remains an area of ongoing investigation. Three randomized trials demonstrated that immediate radiotherapy to the prostate bed in patients with adverse pathologic features significantly improves biochemical outcomes, but with mixed results for the end points of DM and overall survival.[1-3] The SWOG (Southwest Oncology Group) 8794 trial demonstrated that immediate postoperative radiotherapy improved DM and overall survival, whereas the European Organization for Research and Treatment of Cancer 22911 trial did not. Both trials included some patients with a detectable PSA > 0.2 ng/mL (in up to a third of

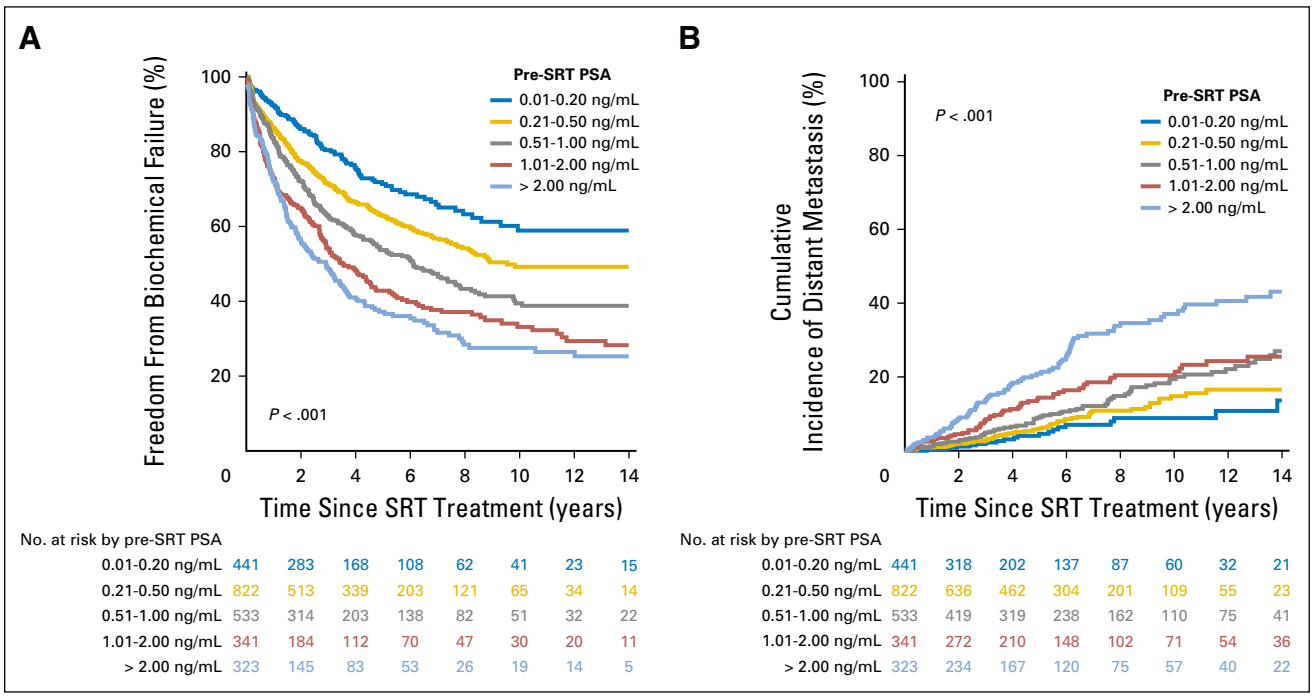

Fig 1. (A) Estimated rates of freedom from biochemical failure by pre-SRT PSA level. (B) Estimated cumulative incidence rates of distant metastases by pre-SRT PSA level. PSA, prostate-specific antigen; SRT, salvage radiotherapy.

Table 2. Estimated Rates of Freedom From Biochemical Failure and Distant Metastases by Gleason Score and Preradiation PSA

PSA (ng/mL)	GS ≤ 6 (grade group 1)			GS 7 (grade group 2-3)			GS 8 (grade group 4)			GS 9-10 (grade group 5)		
	5-yr FFBF (%)	95% CI	No.	5-yr FFBF (%)	95% CI	No.	5-yr FFBF (%)	95% CI	No.	5-yr FFBF (%)	95% CI	No.
0.01-0.1	100	100 to 100	25	82	73 to 91	107	73	47 to 98	22	47	23 to 72	30
0.11-0.2	85	73 to 98	51	64	55 to 74	155	69	47 to 91	25	41	18 to 64	26
0.21-0.5	82	75 to 88	179	62	57 to 66	502	45	1 to 59	68	42	30 to 54	73
0.51-1.0	76	68 to 84	146	49	42 to 55	308	38	18 to 58	37	23	8 to 39	42
1.01-2.0	58	48 to 68	116	35	26 to 44	165	33	17 to 50	45	27	0 to 55	15
> 2.0	52	41 to 63	82	32	23 to 41	150	30	13 to 47	47	26	10 to 43	44
P	< .001			< .001			.013			.049		

PSA (ng/mL)	GS ≤ 6 (grade group 1)			GS 7 (grade group 2-3)			GS 8 (grade group 4)			GS 9-10 (grade group 5)		
	10-yr DM (%)	95% CI	No.	10-yr DM	95% CI	No.	10-yr DM	95% CI	No.	10-yr DM	95% CI	No.
0.01-0.1	0	0 to 0	25	7	0 to 14	107	16	0 to 40	22	23	0 to 45	30
0.11-0.2	0	0 to 0	51	7	0 to 16	155	7	0 to 20	25	32	0 to 68	26
0.21-0.5	3	0 to 8	179	16	10 to 22	502	22	6 to 39	68	29	16 to 43	73
0.51-1.0	3	0 to 7	146	23	16 to 30	308	36	10 to 62	37	37	16 to 58	42
1.01-2.0	10	3 to 17	116	25	17 to 33	165	21	7 to 35	45	40	11 to 69	15
> 2.0	22	12 to 32	82	33	22 to 44	150	62	39 to 85	47	65	45 to 85	44
P	< .001			< .001			.024			.009		

Abbreviations: DM, distant metastases; FFBF, freedom from biochemical failure. GS, Gleason score; PSA, prostate-specific antigen.

cases); therefore, neither trial formally tested the concept of purely adjuvant therapy (for an undetectable PSA) versus salvage therapy. Because adjuvant radiotherapy is associated with a modest increase in toxicity, and because not all patients with adverse pathologic features will experience a recurrence, some investigators have advocated for close postoperative surveillance with initiation of early SRT at the first sign of a detectable PSA.[7,8] Notably, the present analysis did not attempt to address the role of adjuvant radiotherapy at an undetectable PSA level, and prospective trials addressing the question of adjuvant versus early SRT are under way, such as the RADICALS (Radiotherapy and Androgen Deprivation in Combination After Local Surgery) and RAVES (Radiotherapy–Adjuvant Versus Early Salvage) trials.[16,17]

Patients across all GS subgroups had significantly better outcomes with initiation of early SRT at lower PSA levels, supporting data from the SWOG randomized trial, which included patients with adverse pathologic features such as EPE, SVI, or positive surgical margins.[18] Those with lower-grade prostate cancer had more favorable FFBF outcomes and lower DM rates compared with patients with higher-grade disease, although outcomes were still worse when SRT was initiated at higher PSA levels. Inclusion of other clinical factors (eg, life expectancy, comorbidities, PSA kinetics) in decision making may take on greater importance for patients with low-grade disease. Additionally, it may be possible that some patients with low and/or slowly rising PSA values may in fact have persistence or regrowth of benign prostatic tissue, which can also affect clinical decision making and expected outcomes.

There are some limitations to this analysis, as well as certain controversies not addressed within the scope of this retrospective investigation. This series included patients in whom uniform evaluation, treatment, and follow-up were not prescribed prospectively, and the estimated patient outcomes are potentially influenced by selection bias, as with other similar observational studies.[4,5,7-10,14] The study population was treated at various institutions over a 25-year span, including a variety of treatment techniques and PSA assay methods that evolved over time. High-grade cancers (GS, 8 to 10) represented only one fifth of the overall patient cohort, potentially limiting the broad applicability of the

Table 3. Multivariable Analyses for Biochemical Failure and Distant Metastases Using Competing Risk Regression Analysis

	BF			DM		
	HR	95% CI	*P*	HR	95% CI	*P*
ADT: no *v* yes	1.85	1.53 to 2.25	< .001	1.41	1.01 to 1.97	.044
GS: 7 *v* ≤ 6	1.98	1.67 to 2.34	< .001	2.34	1.66 to 3.31	< .001
GS: 8 *v* ≤ 6	2.43	1.93 to 3.06	< .001	3.17	2.06 to 4.89	< .001
GS: 9-10 *v* ≤ 6	3.11	2.39 to 4.03	< .001	5.39	3.49 to 8.32	< .001
EPE: yes *v* no	1.32	1.14 to 1.53	.001	1.19	0.90 to 1.59	.23
Positive margins: yes *v* no	0.71	0.63 to 0.81	< .001	0.69	0.55 to 0.87	.002
SVI: yes *v* no	1.35	1.14 to 1.60	.001	1.87	1.41 to 2.49	< .001
Pre-SRT PSA (per ng/mL)	1.88	1.71 to 2.07	< .001	2.23	1.90 to 2.63	< .001
SRT dose: ≥ 66 Gy *v* < 66 Gy	0.81	0.71 to 0.91	.001	0.97	0.76 to 1.24	.80

Abbreviations: ADT, neoadjuvant/concurrent androgen-deprivation therapy; BF, biochemical failure; DM, distant metastases; EPE, extraprostatic extension; GS, Gleason score; HR, hazard ratio; PSA, prostate-specific antigen; SRT, salvage radiotherapy; SVI, seminal vesicle invasion.

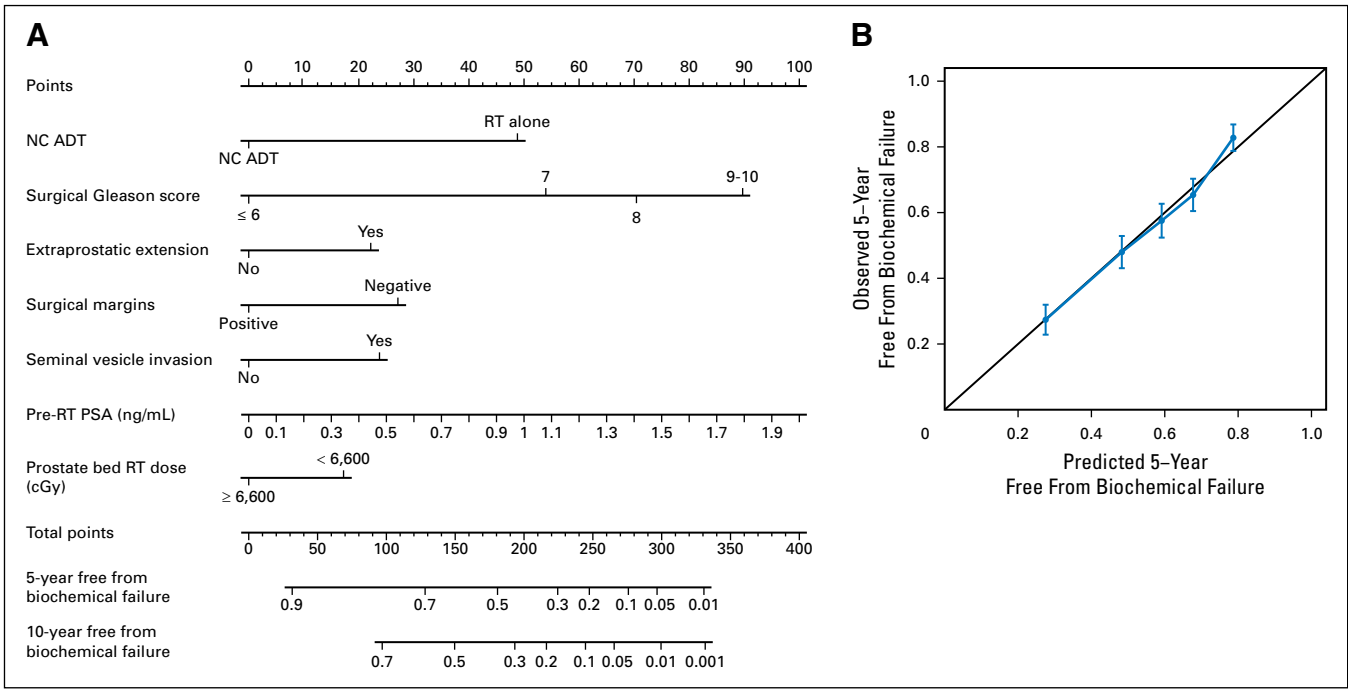

Fig 2. (A) Pretreatment nomogram estimating 5- and 10-year rates of freedom from biochemical failure after salvage radiotherapy. Concordance index, 0.68. Instructions: locate the patient's Gleason score on the respective axis; draw a straight line up to the Points axis to determine how many points toward disease recurrence that the patient receives for the Gleason score; repeat this process for the remaining disease and treatment parameters; sum the points and locate this number on the Total points axis; and draw a straight line down to find the patient's estimated risk of biochemical recurrence. (B) Calibration of the freedom from biochemical failure nomogram. ADT, androgen-deprivation therapy; NC, neoadjuvant/concurrent; PSA, prostate-specific antigen; RT, radiotherapy.

study findings. Patient-reported outcomes and treatment-related toxicity were not available in this cohort, but these issues have been previously addressed in the literature.[19]

We could not determine the optimal integration of ADT with SRT from this analysis, because the utilization of ADT varied widely in this study. However, on multivariable analysis, ADT use was associated with a nearly 50% relative reduction in the risk of FFBF ($P < .001$) and a 30% relative reduction in the risk of DM ($P = .044$). The benefit of ADT with SRT was recently confirmed in two prospective phase III trials. The RTOG (Radiation Therapy Oncology Group) trial 9601 (NCT00002874) reported a benefit in overall survival from the addition of 2 years of the antiandrogen bicalutamide (150 mg once per day) to conventional SRT.[20] Certain subsets appeared to have the greatest benefit from ADT, including those with a GS of 7 to 10, higher PSA values, and positive surgical margins. The Groupe d'Etude des Tumeurs Uro-Génitales 16 randomized trial (NCT00423475) demonstrated a biochemical recurrence benefit to 6 months of luteinizing hormone-releasing hormone agonist therapy in addition to SRT.[21] The recently closed RTOG 0534 trial (NCT00567580) investigated the role of short-term luteinizing hormone-releasing hormone therapy (with an oral antiandrogen) with or without pelvic nodal radiation, and the results will likely guide clinical practice in the future. In the meantime, subset analyses from this multi-institutional cohort are planned to further examine the role of ADT with SRT and better estimate which patients may derive the greatest benefit from combined therapy.

Genomic analyses were not performed on the tumor specimens and thus could not be incorporated into this model. Genomic classifiers have been shown to provide unique prognostic information in addition to traditional clinical parameters and may help to identify patients at higher risk for subsequently developing metastatic disease.[22-24] The impact of PSADT could not be accurately estimated in this predictive model because of the inclusion of patients treated at low PSA levels (as low as 0.01 ng/mL) or with just a single postoperative PSA value before SRT, limiting uniform PSADT determinations in the study cohort. It is reassuring that despite having eliminated PSADT from the contemporary analysis, the concordance index remained robust at 0.68 for the FFBF nomogram (compared with 0.69 in the original nomogram), whereas the DM nomogram had a concordance index of 0.74. On the basis of prior investigations, it should be acknowledged that patients with short PSADT may have worse outcomes than estimated by this updated nomogram, and those patients with a long PSADT may fare better than predicted.[5]

Despite its limitations, this study provides clinicians and patients with a clinically meaningful predictive tool that can aid with joint decision making. Early intervention with SRT (with or without ADT) at detectable PSA levels before exceeding a commonly used threshold dose of 0.2 ng/mL is associated with improved outcomes of FFBF and DM compared with delayed intervention at higher PSA levels. This supports the American Society for Radiation Oncology/AUA consensus statement that postoperative SRT should be administered at the earliest sign of PSA recurrence, and clinicians need not delay SRT solely on the basis of achieving historically traditional definitions of BF (PSA levels exceeding 0.2 ng/mL) after RP. We could not address the potential that adjuvant RT in the absence of a detectable PSA would result in better outcomes;

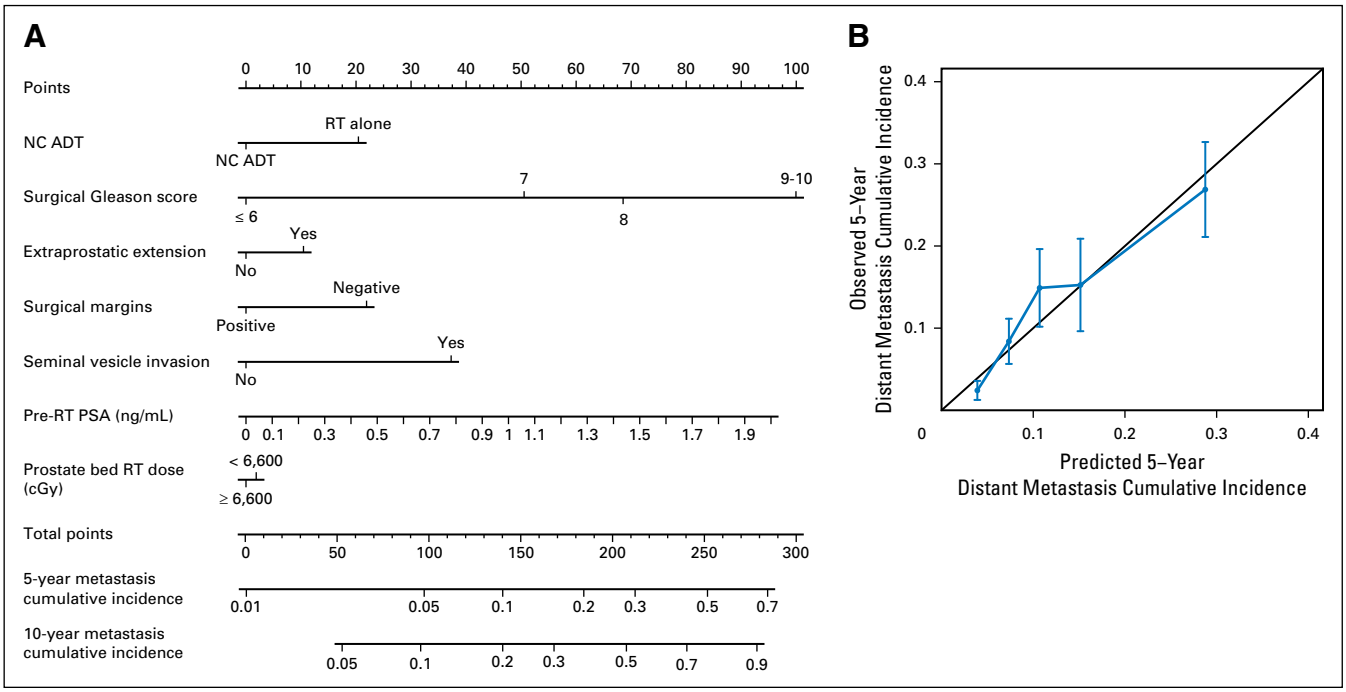

Fig 3. (A). Pretreatment nomogram estimating 5- and 10-year rates of distant metastases after salvage radiotherapy. Concordance index, 0.74. Instructions: locate the patient's Gleason score on the respective axis; draw a straight line up to the Points axis to determine how many points toward disease recurrence that the patient receives for the Gleason score; repeat this process for the remaining disease and treatment parameters; sum the points and locate this number on the Total points axis; and draw a straight line down to find the patient's estimated risk of distant metastases. (B) Calibration of the distant metastasis nomogram. ADT, androgen-deprivation therapy; NC, neoadjuvant/concurrent; PSA, prostate-specific antigen; RT, radiotherapy.

however, ongoing randomized trials are addressing this issue.[16,17] Also, we were not able to address the common practice of delaying radiotherapy to allow for postoperative recovery of urinary incontinence or sexual function, an issue with limited evidence in the literature for which further prospective study is needed. Ultimately, the postoperative management of men with adverse pathologic features and/or a detectable PSA after RP must take into consideration several issues, including life expectancy, quality of life, and the likelihood of tumor control.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Contemporary Update of a Multi-Institutional Predictive Nomogram for Salvage Radiotherapy After Radical Prostatectomy

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

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No relationship to disclose

Shree Agrawal
No relationship to disclose

Tianming Gao
No relationship to disclose

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Consulting or Advisory Role: Medivation/Astellas Pharma, Bayer Healthcare Pharmaceuticals, Genentech

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Research Funding: Janssen Pharmaceuticals
Patents, Royalties, Other Intellectual Property: UpToDate

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Research Funding: Novartis

Felix Y. Feng
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Consulting or Advisory Role: Medivation/Astellas Pharma, GenomeDx, Celgene
Research Funding: Varian Medical Systems, Celgene
Patents, Royalties, Other Intellectual Property: Helped develop molecular signature to predict radiation resistance in breast cancer, which was patented by the University of Michigan and is in the process of being licensed to PFS Genomics (a company author helped to found)

Stanley L. Liauw
No relationship to disclose

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Patents, Royalties, Other Intellectual Property: Patents on software and devices held by the University of Miami (no income)
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Acknowledgment

We acknowledge the following contributors in the data collection process: Chandana Reddy, Rebecca Clayman, Sigolene Galland, Michael Drumm, William Jackson, and Skyler Johnson.