Simplified Predictive Nomogram for Postprostatectomy Patients Treated with High-dose Salvage Intensity Modulated Radiation Therapy

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Research

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Abstract

Purpose:

The role of salvage radiotherapy (RT) is established in prostate cancer patients undergoing radical prostatectomy (RP) with biochemical failure (BCF). Intensity modulated RT (IMRT) is adapted for post-RP treatment. This study aimed to investigate the prognostic factors and develop a nomogram to predict biochemical control in patients treated with exclusively salvage high-dose IMRT for post-RP BCF.

Materials and Methods:

One hundred and eleven patients underwent post-RP IMRT, and 92 patients were enrolled after excluding patients with adjuvant RT or lymph node metastasis on RP. Fifty-two percent of patients had androgen-deprivation therapy (ADT). Moreover, 20% and 34% had pathological T3a and T3b disease, respectively, and 70% had positive surgical margins. The median dose of IMRT was 70 Gy to the prostatic and seminal vesicle bed. Using multivariable Cox regression analysis, a nomogram model was generated to predict the probability of BCF after salvage IMRT.

Results:

The 5-year BCF-free survival (BFFS), metastasis-free survival (MFS), and overall survival (OS) after salvage IMRT were 56%, 89%, and 88%, respectively. Post-RP prostate-specific antigen (PSA) nadir >0.1 ng/ml (p=0.004), PSA >0.5 ng/ml at salvage IMRT (p=0.016), and Gleason score ≥8 (p=0.013) were independent unfavorable prognostic factors for BFFS on multivariate analyses. The use of ADT, T3a/T3b disease, and positive surgical margins were not associated with BFFS. The predictions from the 3-factor nomogram (post-RP PSA nadir, pre-IMRT PSA, and Gleason score) appeared to be discriminative. The concordance index was 0.713, similar to 0.739 from the 7-factor nomogram with the addition of ADT, T3a/3b, positive margins, and IMRT dose ≥70 Gy.

Conclusion:

Salvage IMRT for post-RP BCF achieved a satisfactory outcome. The simplified 3-factor (post-RP PSA nadir, pre-IMRT PSA, and Gleason score) nomogram predicted biochemical control and demanded further validation.

Introduction

Radical prostatectomy (RP) is a common treatment for patients with clinically localized prostate cancer (PCa) and life expectancy > 10 years.[1] Despite significant advances in surgical techniques, including laparoscopic procedures and robotic surgery, greater than half of patients with adverse pathologic features experience biochemical failure (BCF) that manifests initially as an increasing level of serum prostate-specific antigen (PSA).[2–4] Extracapsular extension, seminal vesicle invasion, and close/positive

sk groups.[5]

Salvage radiation therapy (RT) has been one of the curative treatment options for post-RP BCF according to current guidelines.[2] A randomized control trial showed that anti-androgen therapy with radiation therapy further improves cancer control and prolongs overall survival.[6, 7] Intensity-modulated RT (IMRT) with dose escalation results in lower acute and late toxicities compared with conventional RT techniques.[8] Currently, the European Organisation for Research and Treatment of Cancer (EORTC) Radiation Oncology Group guidelines recommend IMRT for primary RT in patients with PCa.[1]

Nomograms are user-friendly methods that are widely used for cancer prognosis to help clinical decision making.[9] Contemporary nomograms to estimate PCa patient outcomes after salvage RT were also established and updated recently.[5] However, nomograms generated from salvage IMRT for BCF are still lacking, especially those with the integration of ADT. In this study, we analyzed the clinical outcomes and investigated the prognostic factors of post-RP patients undergoing salvage high-dose IMRT for BCF and developed a predictive nomogram for the IMRT era.

Material And Methods

Patients

From 2004 to 2015, 111 patients with PCa underwent post-RP IMRT at our institution. The inclusion criteria were patients with PCa who underwent post-RP salvage IMRT for BCF with no detectable gross recurrence or metastasis by digital rectal examination, computed tomography or magnetic resonance imaging of the pelvis/abdomen, and whole body bone scan. Sixteen patients receiving adjuvant post-RP IMRT and three patients with pathologically involved pelvic lymph node(s) on RP were excluded. A total of 92 patients were enrolled in this series. The 7th American Joint Committee on Cancer TNM classification was used for staging the disease at the time of RP. The definition of post-RP BCF was a PSA level of > 0.20 ng/ml detected on two consecutive measurements with an interval of at least 3 months. The study was approved by our Institutional Review Board (201511052RINC).

Treatments

In this analysis, 44 patients underwent retropubic RP, 15 patients had laparoscopic RP, and 33 patients received robotic-assisted RP. All of these patients underwent IMRT, and the median RT dose was 70 Gy (range: 63–74 Gy) with 6-MV or 10-MV photon radiation. For IMRT, the clinical target volume (CTV) consisted of prostatic and seminal vesicle bed plus periprostatic tissues per the EORTC guidelines for target volume definition in postoperative RT for PCa.[10] Planning target volume (PTV) expansions were 6 mm posteriorly (rectum), 6 mm inferiorly, and 10 mm anteriorly, bilaterally, and superiorly from CTV. The treatment goal was 100% of the prescribed radiation dose covering > 95% of the PTV with the maximum dose not exceeding 110% of the prescribed dose. Routine onboard cone-beam computed tomography was used to verify target positions. Androgen-deprivation therapy (ADT) was administered in 48 (52%) patients based mainly on factors associated with high risk, including high nadir PSA after RP, high [illegible]. For patients treated with ADT and IMRT, ADT was

administered as a neoadjuvant more than 2 months prior to RT and was continued concurrently with RT. Alternatively, ADT was administered concurrently with IMRT and maintained after IMRT for 2 years. Patients typically received gonadotropin-releasing hormone (GnRH) agonist as monotherapy. An oral anti-androgen was typically initiated at the start of GnRH agonist therapy to prevent a rebound surge of androgen.

Follow-up

Follow-up duration, survival time, and event time were calculated from the start of salvage IMRT. Kaplan-Meier analysis was performed to determine overall survival (OS), metastasis-free survival (MFS), and BCF-free survival (BFFS) rates. MFS was defined as survival in the absence of clinical metastasis. Treatment-related toxicities were determined using Common Toxicity Criteria v.4.0.

Statistics

Descriptive analysis was performed by calculating ranges, means, medians, and standard deviations. Continuous variables were compared with a two-sided unpaired Student's t-test. Chi-square and Fisher exact tests were used for contingency table analysis. The log-rank test was used to determine prognostic factors affecting survival. All prognostic variables found to be significant or borderline significant in univariate analysis were included in multivariate analysis using the Cox proportional hazards regression model. Statistical significance was defined as $P < 0.05$. All statistics were performed with IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, NY, USA), and a nomogram was generated using the R software environment for statistical R (computing and graphics (version 3.3.0; http://www.r-project.org/). The model-predicted risks were pooled into groups by deciles, and the means and the standard deviations of the model-predicted risks for each group were calculated. Calibration was assessed by plotting the observed risk versus model-predicted risk of BCF among the patients.

Results

Patient characteristics

The median age at the time of RP was 63 years (range: 41–76), and that at salvage IMRT was 66 years (range: 42–84). A total of 30 patients had initial clinical T1 (33%), 56 had T2 (56%), and 6 had T3 disease (11%). Sixteen patients (17%) had a Gleason score of 6, 44 (48%) had a score of 7, 9 (10%) had a score of 8, and 20 (22%) had a score of 9. Three patients had pathological T1 disease (3%) after RP, 38 had T2 (41%), 50 had T3 (54%) and one had T4 (1%). All enrolled patients completed a full course of high-dose IMRT within 8 weeks smoothly. Their baseline characteristics are shown in Table 1.

Survival outcomes

With a median follow-up time of 56 months (range: 32–160 months), the 5-year OS, MFS, and BFFS of these patients after salvage IMRT were 88%, 89%, and 56%, respectively (Fig. 1). During follow-up, 10 patients died, 9 patients experienced distant metastasis, and 2 patients had both local recurrence and

distant metastasis. There were 38 patients with BCF after salvage IMRT. The median BFFS time was 30 months (range: 2-149 months).

Adverse effects

Acute and chronic genitourinary (GU) or gastrointestinal (GI) toxicity are shown in Table 2. Two patients (2.2%) experienced grade 2 late GI toxicity, and 2 patients (2.2%) had grade 3 toxicity. Five patients had urinary incontinence requiring absorbent pads before salvage IMRT. In total, six patients (6.5%) experienced grade 2 late GU toxicity, and five patients (5.4%) had grade 3 toxicity.

Prognostic factors

On univariate analysis, patients with a post-RP PSA nadir ≤ 0.1 ng/ml (P = 0.005), PSA at salvage IMRT ≤ 0.5 ng/ml (P = 0.018), and Gleason score ≤ 7 (P = 0.041) had significantly better BFFS. Pathological T stage, Gleason score, ADT use and duration at the time of BCF, the interval from RP to BCF, salvage IMRT dose, and surgical margin status on RP were not significantly associated with BFFS. In multivariate analysis, post-RP PSA nadir (P = 0.004), PSA at salvage IMRT (P = 0.016), and Gleason score (p = 0.013) were identified as statistically significant independent factors for BFFS (Table 3). Patients with favorable prognosticators, including post-RP PSA nadir ≤ 0.1 ng/ml, PSA at salvage IMRT ≤ 0.5 ng/ml, and Gleason score ≤ 7, had a 5-year BFFS of 72% compared with 48% for other patients (P = 0.009) (Fig. 2). On univariate analyses, patients with PSA at salvage IMRT > 0.5 ng/ml (P = 0.033) as the only significant factor had worse MFS (supplementary figure), but no significant factor was associated with OS.

Nomogram development

A nomogram was developed with 7 factors selected on the basis of their known prognostic significance from previous related studies, including post-RP PSA nadir, pathological T stage on RP, Gleason score, pre-RT PSA, surgical margins, ADT at BCF, and IMRT dose.[5, 11] The concordance index was 0.739. After simplifying the nomogram by integrating only the three factors with statistical significance (post-RP PSA nadir, Gleason score, pre-RT PSA), the concordance index was 0.713. Figure 3 depicts the predictive nomogram and calibration plots for the outcomes of BFFS.

Patients were randomly divided into two subsets. Specifically, 62 patients were assigned to the training set, and 30 patients were assigned to the validation set. The baseline characteristics of the patients between the training and validation sets were not different based on the chi-squared test for categorical variables and Student's t-test for continuous variables (Supplementary Table 1).

Discussion

Our study demonstrates that among post-RP patients with BCF exclusively treated by salvage high-dose IMRT, 52% of those treated with ADT achieved good clinical outcome. The low-risk patients were well stratified by three prognostic factors. Patients who had a post-RP PSA nadir ≤ 0.1 ng/ml, PSA level ≤ 0.5 ng/ml before salvage IMRT, and Gleason score ≤ 7 had a 5-year BFFS of 83%. The concordance index

of 0.713 from such a simplified 3-factor nomogram was similar to 0.739 from the 7-factor nomogram, which included ADT use, surgical margins, T3a/T3b disease, and IMRT dose.

The optimal post-RP management of men with PCa remains debatable between adjuvant RT and salvage RT. Randomization trials on adjuvant RT revealed the benefit of disease control and survival[4], but trials on direct comparison are still ongoing.[12] Here, we showed the promising outcome that early salvage RT in our cohort balances toxicity and disease control. A previous study showed approximately 50% biochemical control at 5 years after salvage RT,[13] and our cohort similarly exhibited a 56% control rate. This finding is similar to the RTOG 9601 study with a median RT dose of 64.8 Gy, and late grade 3 GU toxicity rates of 7.0% and 6.0% for patients treated with RT and bicalutamide versus RT alone,[6], respectively. In our series, the late GU toxicity rate was 5% with a median RT dose of 70 Gy.

IMRT provides an effective technique for dose escalation and reduction of adverse effects. The Memorial Sloan-Kettering Cancer Center compared the toxicity between three-dimensional RT and IMRT and found IMRT to be independently associated with a reduction of ≥ grade 2 GI toxicity compared with three-dimensional RT (1.9% vs. 10.2%)[14]. Recently, Hoffman et al. showed superior cancer control for men with localized PCa who received dose-escalated moderately hypofractionated IMRT.[15] Our data on patients exclusively receiving high-dose IMRT did not reveal an association between RT dose and biochemical control probably due to the uniform IMRT technique and the lack of a low-dose subgroup.

Based on updated data from the GETUG-AFU 16 trial, the additional use of 6-month ADT to salvage RT significantly improved MFS[16]. However, none of the clinical factors reached a significant level of association with MFS. In comparison, the survival benefit of 24-month bicalutamide from the subgroup analysis from the RTOG 9601 trial was not significant in patients with early salvage RT (PSA ≤ 0.6 ng/ml)[17]. Both studies emphasized the differential effects of ADT between the subgroups of patients undergoing salvage RT. Notably, our data indicated that patients with PSA at salvage IMRT >0.5 ng/ml were associated with significantly worse MFS, but no prognosticator was associated with OS. Approximately two-thirds of our patients with PSA <0.5 ng/ml at the time of salvage RT and 52% of patients in this study receiving ADT might explain the similar impact on MFS and insignificant association with OS.

Our study showed that post-RP nadir, PSA level at salvage IMRT, and Gleason score were prognostic factors, and these findings were consistent with other series. Goenka et al. demonstrated that a pre-RT PSA > 0.4 ng/ml was an independent prognostic factor[18], and Doherty et al. reported that patients with undetectable PSA after RP had better relapse-free survival[19]. The updated data by Stephenson et al. on 2,460 patients receiving traditional RT with doses greater than or equal to 66 Gy demonstrated pre-RT PSA, Gleason score, extraprostatic extension, seminal vesicle invasion, surgical margins, ADT use, and salvage RT dose associated with BFFS. Patients across all Gleason score subgroups had significantly better outcomes with the initiation of early salvage RT at lower PSA levels.[5]

Nomograms have been widely used for different cancers and related outcomes.[20, 21] One nomogram with a promising c-index could be a useful and convenient tool for individualized cancer prognoses.

Simplified nomograms have also been reported for various clinical applications.[22, 23] Our simplified 3-factor nomogram integrated with the post-RP PSA nadir, pre-IMRT PSA, and Gleason score could provide a more convenient tool for in-time decision making and outcome prediction.

Our study has some limitations. The retrospective analysis of a relatively small number of patients inevitably has selection bias and confounded data interpretation. In addition, inhomogeneous use of ADT in this study could also cause deviation of the clinical findings. However, the inconclusive evidence-based benefit of ADT in patients treated with salvage RT for BCF before 2015 may explain this situation in clinical practice. Finally, the evolved surgical techniques in the study period might have uncertain impact on the risk of post-RP BCF and the effect of salvage treatment. Despite these limitations, the generated nomogram may provide a simple tool to evaluate the probability of biochemical control in daily practice.

In conclusion, salvage 70-Gy IMRT for patients with post-RP BCF achieved a satisfactory outcome and low toxicity. The simplified 3-factor (post-RP PSA nadir, pre-IMRT PSA, Gleason score) nomogram developed from this patient cohort predicted biochemical control and demands further validation.

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Tables

Table 1
Clinical characteristics of 92 post-prostatectomy prostate cancer patients with biochemical failure undergoing salvage intensity modulated radiation therapy (IMRT)

Variable	Patient number	Percent
Total	92	100
Age at IMRT		
< 65	38	41.3
65–75	47	51.1
> 75	7	8.2
Initial clinical T stage before RP		
T1	30	32.6
T2	56	60.9
T3	6	6.5
Pathological T stage on RP		
T1	3	3.3
T2	38	41.3
T3	50	54.3
T4	1	1.1
Gleason score on RP		
6	16	17.4
7	46	50
8	10	10.9
9	20	21.7
Surgical margin		
Positive	64	70.0
Negative	28	30.4
PSA before RP		
< 10 ng/ml	34	37.0

Variable		Patient number	Percent
	10–20 ng/ml	32	34.8
	> 20 ng/ml	26	28.3
Surgical type			
	Retropubic RP	44	47.8
	Laparoscopic RP	15	16.1
	Robotic RP	33	35.5

Variable	Patient number	Percent
PSA nadir after RP		
<0.1 ng/ml	48	52.1
0.1-0.2 ng/ml	21	22.8
0.2-0.5 ng/ml	12	13.0
>0.5 ng/ml	11	12.0
PSA before salvage IMRT		
<0.2 ng/ml	20	21.7
0.2-0.5 ng/ml	37	40.2
>0.5 ng/ml	35	38.0
IMRT dose		
60-63.9 Gy	12	13.0
64-67.9 Gy	12	13.0
68-69.9 Gy	1	1.1
70-74 Gy	67	72.8
ADT at biochemical failure		
Yes	48	52.1
No	44	47.8
Duration of ADT		
≤ 6 months	16	33.3
6-12 months	8	16.7
12-24 months	16	33.3
24-36 months	8	16.7
ADT: androgen deprivation therapy; IMRT: intensity-modulated radiation therapy; PSA: prostate specific antigen; RP: radical prostatectomy		

Table 2
Acute and chronic gastrointestinal (GI) and genitourinary (GU) toxicity of post-radical prostatectomy patients who underwent salvage intensity modulated radiation therapy

Variable		Grade 0(%)	Grade 1(%)	Grade 2(%)	Grade 3(%)	Grade 4(%)
GI toxicity						
	Acute	51 (55)	36 (39)	5 (5)	0 (0)	0 (0)
	Late	79 (86)	9 (10)	2 (2)	2 (2)	0 (0)
GU toxicity						
	Acute	59 (64)	28 (30)	5 (5)	0 (0)	0 (0)
	Late	71 (77)	10 (11)	6 (7)	5 (5)	0 (0)

Table 3

Univariate and multivariate analyses of the prognostic factors on biochemical failure-free survival (BFFS) of post-radical prostatectomy (RP) patients with biochemical failure undergoing salvage intensity modulated radiation therapy (IMRT)

Variable		Univariate		Multivariate	
		5-year BFFS	*p* value	HR (95% CI)	*p* value
PSA at salvage IMRT					
	>0.5 ng/ml	35.50%	0.018	2.16(1.123-4.157)	0.016
	≤0.5 ng/ml	67.00%			
PSA nadir after RP					
	>0.1 ng/ml	43.60%	0.005	2.87 (1.463-5.609)	0.004
	≤0.1 ng/ml	66.00%			
Pathological T stage					
	T3-T4	50%	0.807		
	T1-T2	57%			
Gleason score					
	8-10	42.00%	0.041	2.27 (1.175-4.388)	0.013
	≤7	61.40%			
Initial PSA before RP					
	≥20 ng/ml	67%	0.831		
	<20 ng/ml	56%			
Androgen-deprivation therapy use at biochemical failure					
	Yes	58.20%	0.901		
	No	50.60%			
Salvage IMRT dose					
	<70 Gy	67.60%	0.084		
	≥70 Gy	49.50%			
Surgical margin on RP					
	Positive	58.70%	0.145		
	Negative	49.50%			

ADT duration			
	≦6 months	72.90%	0.451
	> 6 months	61.90%	
ADT: androgen-deprivation therapy; CI: confidence interval; HR: hazard ratio; IMRT: intensity modulated radiation therapy; PSA: prostate specific antigen; RP: radical prostatectomy			

Figures

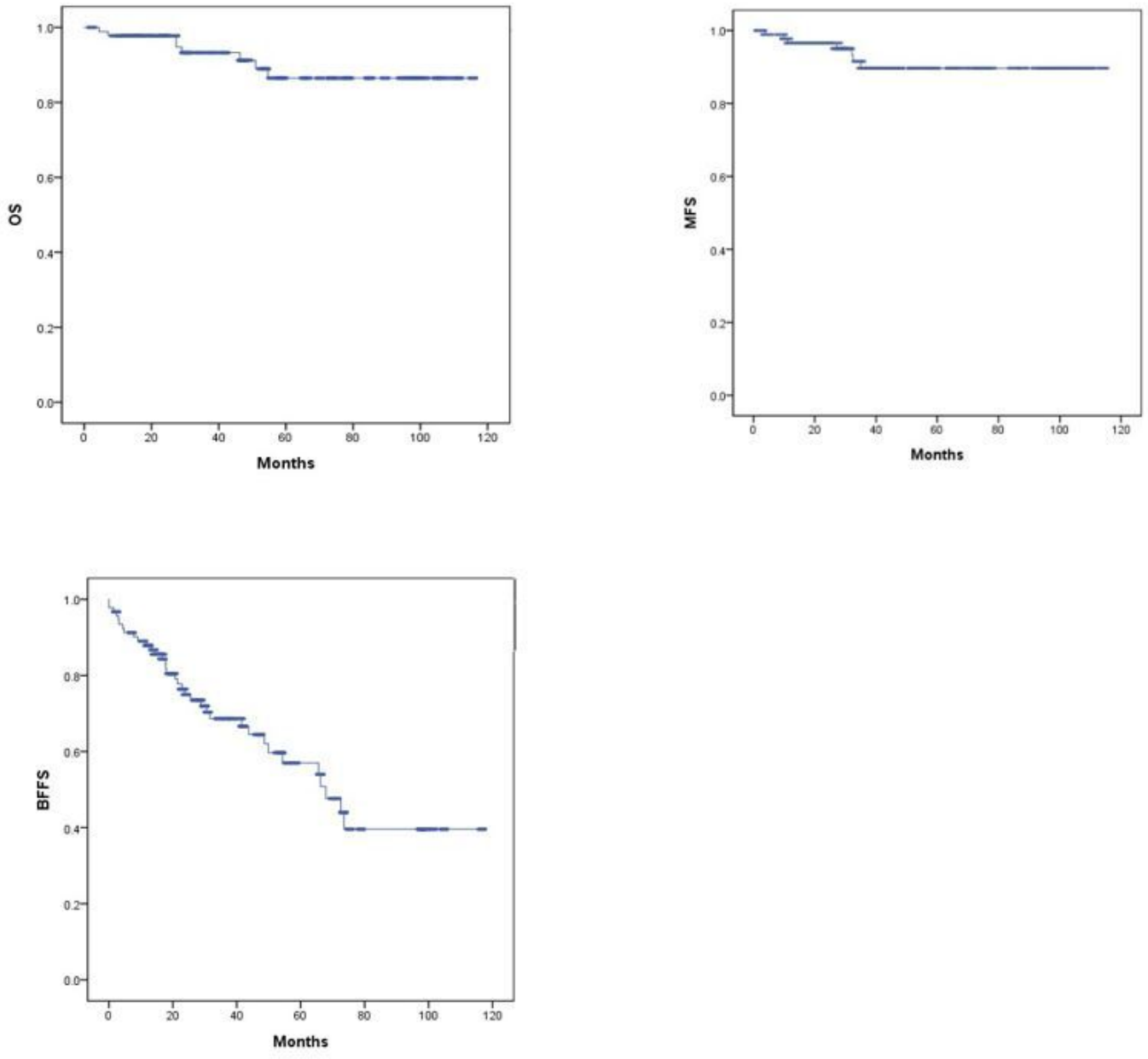

Figure 1

(A) Overall survival (OS), (B) metastasis-free survival (MFS), and (C) biochemical failure-free survival (BFFS) of 92 patients undergoing salvage intensity-modulated radiation therapy for post-prostatectomy biochemical failure.

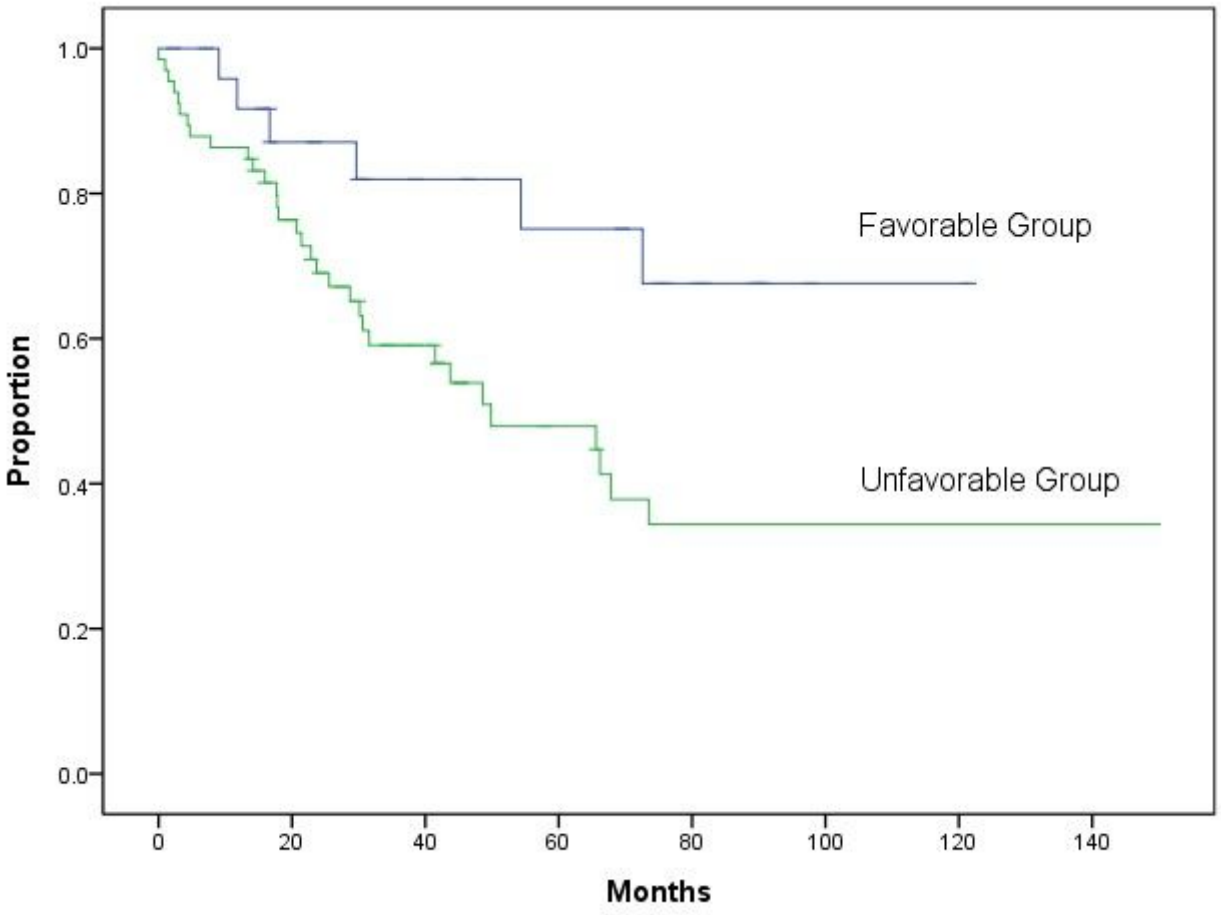

Figure 2

Biochemical failure-free survival (BFFS) between patients with post-radical prostatectomy (RP) PSA nadir ≤0.1 ng/ml, PSA ≤0.5 ng/ml at salvage intensity modulated radiation therapy (IMRT), and Gleason score ≤7 (favorable group) compared with other patients (unfavorable group) (P=0.009).

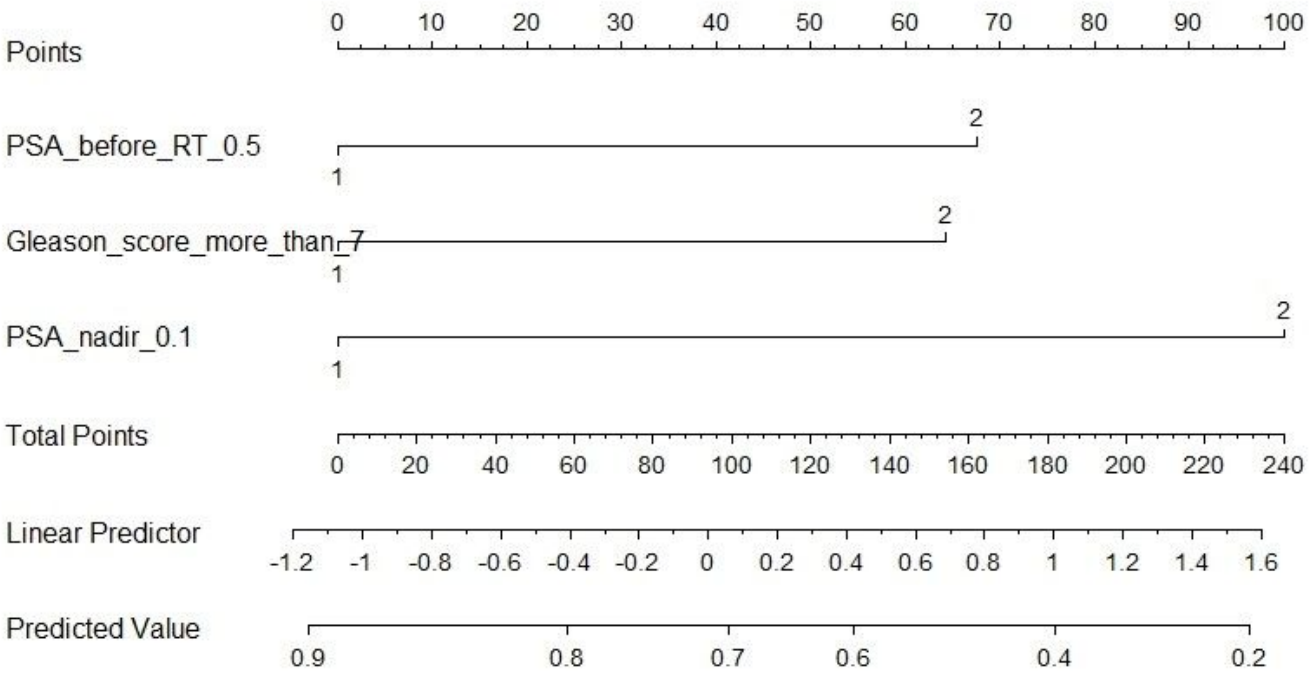

Figure 3

Predictive nomogram estimating the 5-year rates of freedom from biochemical failure of patients with post-prostatectomy biochemical recurrence treated with salvage intensity-modulated radiation therapy

Supplementary Files

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- SupplementaryTable1.docx
- SupplementaryTable1.docx