ORIGINAL RESEARCH

Multivariate Analysis of Factors Affecting Biochemical Recurrence After Radical Prostatectomy

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Objective: This study aims to evaluate the effects on biochemical recurrence (BCR) of the following proposed prognostic factors after radical prostatectomy (RP): patients' clinical T stage, Gleason grade group (GG) of RP specimen, technique of operation used (open RP vs. robot-assisted laparoscopic RP), presence of positive surgical margin (PSM), length of PSM, GG at PSM, extraprostatic extension (EPE) at PSM, and presence of detectable PSA at 4-6 weeks after RP. It also aims to identify which among the aforementioned variables are independent predictors of risk for BCR.

Patients and Methods: This is a retrospective study. Included in the study were patients who underwent RP (Open and Robot-assisted Laparoscopic technique) at two tertiary hospital branches of an academic medical center from April 2009 to December 2015 with histopathology reports read by a single urologic pathologist and with complete follow- up for at least one year. Excluded were those who underwent RP but without complete follow- up. Using Pearson chi-square and z-test with level of significance set at 0.05, the clinicopathologic variables including: patients clinical stage, GG of RP specimen, length of PSM, GG at positive margins, presence of EPE at positive margins, and presence of detectable PSA after the surgery were assessed in order to know which among these factors were predictive of BCR. Multinomial regression analysis was also used to identify which among the variables were independent predictors of risk for BCR.

Results: A total of 165 patients underwent RP from April 2009 to December 2015, among which 72 patients were eligible for inclusion in the final analysis. Clinical T2 stage was found to be a predictor of BCR with odds ratio of 13.000 (95%CI: 3.705 - 45.620; $p < 0.001$) as compared to stage T1. GG of final histopathology report of prostatectomy specimen was found to be a predictor of BCR, as those with grade groups 4 and 5 had significantly increased risk of BCR with odds ratio of 70.778 (95%CI: 8.207 - 610.426; $p < 0.001$) as compared to those with grade groups 1 to 3. Patients with positive margins had increased risk of BCR, with odds ratio of 13.458 (95%CI: 13.472 - 52.171; $p < 0.001$) compared to those with negative margins. GG at the PSM was found to be a predictor of BCR, with a grade grouping of 4 or 5 at the positive margin predicting BCR with odds ratio of 20.625 (95%CI: 2.241 - 189.847; $p = 0.008$) as compared to grade grouping of 1 or 2 at the margin. Detectable PSA after RP was found to be a predictor of BCR, with odds ratio of 115.000 (95%CI: 19.457 - 679.712; $p < 0.001$) as compared to undetectable PSA after RP. Technique of RP ($p = 0.177$), measured length of PSM ($p = 0.713$), and EPE at PSM ($p = 0.146$) were not found to predict BCR. Furthermore, clinical T stage ($p = 0.007$) and detectable PSA after RP ($p < 0.001$) were found to be independent predictors of BCR among the risk factors examined.

Conclusion: Of the independent variables examined, clinical T stage, GG of RP specimen, presence of PSM, GG at positive margins, and detectable PSA were found to be significant predictors of BCR.

Technique of RP, measured length of PSM, and EPE at PSM were not found to predict BCR. Furthermore, multivariate analysis showed that only clinical T stage and detectable PSA after RP were independent predictors of BCR. Attentive assessment of these predictors in the preoperative period should aid the urologist in clinical decision-making and in advising patients regarding their prognosis.

Keywords: Biochemical recurrence, medical prostatectomy, prostate specific antigen

Introduction

Prostate cancer is the most common solid tumor in males, with an incidence of 123.2 cases per 10,000 men of all races combined in a North American population, and 96.0 cases per 100,000 adjusted person-years in a European population. It is also the third leading cause of cancer-related deaths in males in both the USA and Europe, after lung and colorectal malignancies.[1,2] Radical prostatectomy (RP) is recognized as the standard of treatment for organ-confined prostate adenocarcinoma in patients with a life expectancy of at least 10 years.[3] However, cure is not achieved in all patients after RP. Biochemical recurrence (BCR) is observed in up to 35% of patients within 10 years, postoperatively.[4]

A retrospective review done by Johns Hopkins researchers involving 1,997 men undergoing RP found that after a mean follow-up of 5.3 years, BCR was observed in 15% of these patients at a median time of 2.3 years. The likelihood of metastatic disease was 37% in 5 years among men who had presented BCR, and 44% of patients with metastatic disease died due to prostate cancer.[5]

Urologists are often faced with the task of outlining the post-surgical prognosis of prostate adenocarcinoma to patients, their families, and other members of an interdisciplinary medical team. The purpose of this study is to investigate clinical and histopathologic variables that have previously been hypothesized to affect risk of BCR after RP.

This study aims to evaluate the effects on BCR of the following proposed prognostic factors after RP: patients clinical T stage, GG of final histopathology report of prostatectomy specimen, technique of operation used (open vs. robot-assisted), presence of PSM, length of PSM, GG of PSM, EPE at PSM, and presence of detectable PSA at 4-6 weeks after RP. Additionally, the study aims to identify which among the aforementioned variables are independent predictors of risk for BCR.

Patients and Methods

This is a retrospective study. Included in this study are those who underwent RP (open technique and robot-assisted laparoscopic technique) at two tertiary hospital branches of an academic medical center from April 2009 to December 2015 with histopathology reports read by a single urologic pathologist and with complete follow- up for at least one year. Excluded were those who underwent RP but without complete follow- up.

Clinicopathologic data collected were patients clinical stage, Gleason grade of RP specimen, length of PSM, presence of EPE at positive margins, Gleason grade at positive margins, PSA nadir after surgery, and follow- up PSA at 3 months, 6 months, and 1 year after surgery.

Presence of PSM on histopathology report, as read by a single urologic pathologist, is defined as cancer cells at the inked margin and was described based on the length in millimeters and character of margin. The area where positive margin was noted and the Gleason score of the margin were considered in the study.

Follow- up PSA results were recorded at 4 weeks post- op, 3 months, 6 months, and 1 year to note for BCR. BCR was the outcome variable and was defined by the American Urological Association (AUA) guidelines panel ultimately as PSA value of 0.2 ng/mL or greater with a second confirmatory laboratory value which is also adopted by the European Guidelines on Prostate Cancer.[6]

GG is assigned as follows, according to the most recent National Comprehensive Cancer Network (NCCN) Prostate Cancer guideline [Table 1].[7]

Table 1. Gleason Grade (GG) grouping based on Gleason score

Gleason score ≤ 6	Group 1
Gleason score 3 + 4 = 7	Group 2
Gleason score 4 + 3 = 7	Group 3
Gleason score 8	Group 4
Gleason score 9-10	Group 5

Using Pearson chi-square and z-test with level of significance set at 0.05, the clinicopathologic variables including patients clinical stage, prognostic grade of RP specimen, technique of operation, length of PSM, presence of EPE at PSM, GG at PSM, and presence of undetectable PSA after the surgery were assessed in order to know which among these factors were predictive of BCR.

Multinomial regression analysis was also used to identify which among the variables were independent predictors of risk for BCR.

Results

A total of 165 patients underwent RP from April 2009 to December 2015. Of the 165 patients, only 72 were included in the study and 93 patients were excluded due to incomplete follow- up. Out of the 72 patients, 13 underwent open radical retropubic prostatectomy while 59 underwent robot-assisted laparoscopic prostatectomy. Of the 72 patients, 54 (75.00%) were clinical T1 while 18 (25.00%) patients were clinical T2.

PSM were noted on final histopathology reports of 35 (48.61%) patients while 37 (51.39%) patients had negative surgical margins. Of the 35 PSM, length of margin was noted to be <3mm in 12 (34.29%) patients, while 23 (65.71%) of them had positive margin length of >3mm. The GG at positive margins were also taken into consideration. Of the 35 with positive margins, 13 (37.14%) patients had GG I at the margin, 10 (28.57%) had GG II, none had GG III, and 12 (34.29%) had GG IV to V. Among the 35 with PSM, 20 (44.44%) patients had PSM at an area of EPE.

Of the total 72 patients included in the study, only 48 (66.67%) patients had undetectable PSA after surgery. PSA was still detectable in 24 (33.33%) patients.

A summary of all the individual factor analyses is shown on Table 9.

Clinical T2 stage was found to be a predictor of BCR with odds ratio of 13.000 (95%CI: 3.705 - 45.620; p < 0.001) as compared to stage T1 [Tables 2.1 & 2.2].

Table 2.1. Clinical T stage as predictor for BCR -- Crosstabulation

		Clinical Stage		Total
		T1	T2	
Biochemical Recurrence	No Recurrence	45	5	50
	With BCR	9	13	22
Total		54	18	72

Table 2.2. Clinical T stage as predictor for BCR -- Significance

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-square	19.636[a]	1	.000	.000	.000
Continuity Correction	17.105	1	.000		
Likelihood Ratio	18.701	1	.000	.000	.000
Fisher's Exact Test				.000	.000
No. of Valid Cases	72				

Gleason grade of final histopathology report of prostatectomy specimen was found to be a predictor of BCR [Tables 3.1 & 3.2]. Patients with GG IV and V had significantly increased risk of BCR with odds ratio of 70.778 (95%CI: 8.207 - 610.426; $p < 0.001$) as compared to those with grade group I to III.

Technique of operation-- open radical retropubic prostatectomy as opposed to robot-assisted laparoscopic RP-- was not found to be significantly different with respect to BCR [Tables 4.1 and 4.2]. Secondarily, technique of operation was also analyzed with respect to presence or absence of positive surgical margin, and was not found to have a significant effect [Tables 4.3 & 4.4].

Table 3.1. GG of RP specimen as predictor for BCR -- Crosstabulation

		GG of Prostatectomy Specimen				
		I	II	III	IV and V	Total
Biochemical Recurrence	No Recurrence	13	25	11	1	50
	With BCR	0	8	1	13	22
Total		13	33	12	14	72

Table 3.2. GG of RP specimen as predictor for BCR -- Significance

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)
Pearson Chi-square	34.742[a]	3	.000	.000
Likelihood Ratio	37.988	3	.000	.000
Fisher's Exact Test	33.147			.000
No. of Valid Cases	72			

Table 4.1. Surgical Technique as predictor for BCR -- Crosstabulation

		Technique		
		Robotic	Open	Total
Biochemical Recurrence	No Recurrence	43	7	50
	With BCR	16	6	22
Total		59	13	72

Table 4.2. Surgical technique as predictor for BCR -- Significance

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)
Pearson Chi-square	1.819[a]	1	.177	.197
Continuity Correctionb	1.033	1	.310	
Likelihood Ratio	1.724	1	.189	.319
Fisher's Exact Test				.197
No. of Valid Cases	72			

Table 4.3. Surgical technique as predictor for PSM -- Crosstabulation

		Presence or Absence of Positive Margin		Total
		Negative	Positive	
Technique	Robotic	32	27	59
	Open	5	8	13
Total		37	35	72

Table 4.2. Surgical technique as predictor for PSM -- Significance

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-square	1.061[a]	1	.303		
Continuity Correction[b]	.524	1	.469		
Likelihood Ratio	1.067	1	.302		
Fisher's Exact Test				.367	.235
No. of Valid Cases	72				

Presence of PSM was found to be a predictor of BCR. [Tables 5.1 & 5.2]. Patients with positive margins had increased risk of BCR, with odds ratio of 13.458 (95%CI: 13.472 - 52.171; $p < 0.001$) compared to those with negative margins. However, among those with positive margins, the measured length of the PSM was not found to predict BCR, >3mm positive margin having an odds ratio of 1.300 (95%CI: 0.321 - 5.272; $p = 0.713$) compared to <3mm positive margin.

Table 5.1. Length of PSM as predictor for BCR -- Crosstabulation

		Length of Positive Margin			
		<3mm	>3mm	Negative Margins	Total
Biochemical Recurrence	No Recurrence	6	10	34	50
	With BCR	6	13	3	22
Total		12	23	37	72

Table 5.2. Length of PSM as predictor for BCR -- Significance

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)
Pearson Chi-square	18.233[a]	2	.000	.000
Likelihood Ratio	19.680	2	.000	.000
Fisher's Exact Test	19.055			.000
No. of Valid Cases	72			

GG at the PSM was found to be a predictor of BCR. [Tables 6.1 and 6.2]. Furthermore, a grade grouping of IV or V at the positive margin predicted BCR with odds ratio of 20.625 (95%CI: 2.241 - 189.847; p = 0.008) compared to grade grouping of I or II at the margin. There were no patients with a GG III tumor at the PSM in this data set.

EPE at the PSM was not found to be a predictor of BCR. [Tables 7.1 & 7.2] Those with EPE at PSM had an odds ratio of 2.786 (95%CI: 0.699 - 11.101; p = 0.146) compared to those with PSM but without EPE.

Table 6.1. GG at PSM as predictor for BCR -- Crosstabulation

			GG at Positive Margin			
		Negative Margins	I	II	IV and V	Total
Biochemical Recurrence	No Recurrence	34	10	5	1	50
	With BCR	3	3	5	11	22
Total		37	13	10	12	72

Table 6.2. GG at PSM as predictor for BCR -- Significance

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)
Pearson Chi-Square	32.031[a]	3	.000	.000
Likelihood Ratio	33.016	3	.000	.000
Fisher's Exact Test	31.253			.000
No. of Valid Cases	72			

Table 7.1. EPE at PSM as predictor of BCR -- Crosstabulation

		Extraprostatic Extension at Positive Margin			
		No Extraprostatic Extension	With Extraprostatic Extension	Negative Margins	Total
Biochemical Recurrence	No Recurrence	9	7	34	50
	With BCR	6	13	3	22
Total		15	20	37	72

Table 7.2. EPE at PSM as predictor of BCR -- Significance

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)
Pearson Chi-square	20.599[a]	2	.000	.000
Likelihood Ratio	21.720	2	.000	.000
Fisher's Exact Test	20.977			.000
No. of Valid Cases	72			

Detectable PSA after RP was found to be a predictor of BCR, with odds ratio of 115.000 (95%CI: 19.457 - 679.712; $p < 0.001$) as compared to undetectable PSA after RP [Tables 8.1 & 8.2].

Among the factors examined, clinical T stage, GG of RP specimen, presence of PSM, GG at positive margins, and detectable PSA were found to be significant predictors of BCR [Table 9].

Table 8.1. Detectable PSA after RP as predictor of BCR -- Crosstabulation

		Undetectable PSA		
		PSA still detectable after RP	PSA falls to undetectable after RP	Total
Biochemical Recurrence	With BCR	20	2	22
	Without BCR	4	46	50
Total		24	48	72

Table 8.2. Detectable PSA after RP as predictor of BCR -- Significance

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)
Pearson Chi-square	47.258[a]	1	.000	.000
Continuity Correction	43.601	1	.000	
Likelihood Ratio	50.377	1	.000	.000
Fisher's Exact Test				.000
No. of Valid Cases	72			

Table 9. Summary of odds ratios and significance of factors

Factor	Odds Ratio	95% Confidence Interval	Significance
Clinical T Stage (T2 or higher vs. T1)	13.000	3.705 - 45.620	<0.001
GG of RP Specimen (IV or V vs. I to III)	70.778	8.207 - 610.426	<0.001
Surgical Technique (Open vs. Robotic)	2.304	0.672 - 7.899	0.184
Presence of PSM (Positive margins vs. Negative)	13.458	13.472 - 52.171	<0.001
Length of PSM (>3mm vs. <3mm)	1.300	0.321 - 5.272	0.713
GG at PSM (IV or V vs. I to III)	20.625	2.241 - 189.847	<0.001
EPE at PSM (With EPE vs Without EPE)	2.786	0.699 - 11.101	0.146
Detectable PSA after RP (Detectable vs. Undetectable)	115.000	19.457 - 679.712	<0.001

Multivariate analysis was done with multinomial regression, examining the effects of clinical T stage, GG of RP specimen, length of PSM, GG at PSM, EPE at PSM, and detectable PSA after RP, on BCR [Table 10]. Clinical T stage ($p = 0.007$) and detectable PSA after RP ($p < 0.001$) were found to be independent predictors of BCR among the risk factors examined.

Discussion

RP is one of the most common treatment modalities for localized prostate cancer and a good surgical outcome after RP always has been the eradication of disease while maintaining continence and potency. To achieve the goal of cancer control, it always has been important to achieve negative surgical margins, because this is an established predictor of biochemical failure.[8]

Pierorazio, et al. proposed a prognostic grouping of Gleason scores that stratified patients into five groups according to their Gleason grade, based on analysis of data from 7869 patients extracted from the Johns Hopkins RP Database.[8] In this study, it was shown that the GG of the final histopathology report of the prostatectomy specimen is a predictor of BCR ($p < 0.001$). Furthermore, BCR was noted in 13 out of 14 patients (92.86%) with grade group IV or V; while none of the 13 patients with grade group I had BCR. The most recent updates of the NCCN Prostate Cancer guideline have adopted this grade grouping for prognostic staging.[7]

Despite refinements in surgical technique and improved patient selection, approximately 25% to 41% of men will develop prostate-specific antigen (PSA) recurrence 10 years after surgery.[10,11,12] In the aforementioned results, it was shown that there was no statistical significant difference on risk for BCR in patients who underwent open prostatectomy and robotic assisted prostatectomy. This could be attributed to the lack of tactile feedback from operating with robotic platform offsetting the advantage of improved visualization.[13,14] It is clear that not all men with a detectable PSA level after surgery are destined to clinical progression, defined as development of metastatic disease, need for

Table 10. Multinomial regression analysis

Likelihood Ratio Tests

Effect	Model Fitting Criteria -2 Log Likelihood of Reduced Model	Likelihood Ratio Tests Chi-Square	df	Sig.
Intercept	3.008[a]	.000	0	.
Clinical Stage	10.265	7.257	1	.007
GG of Prostatectomy	9.888	6.880	3	.076
Length of Positive Margin	5.781	2.773	1	.096
GG at Positive Margin, Clustered	4.055	1.046	2	.593
EPE at Positive Margin	6.726	3.718	2	.156
Detectable PSA	32.138	29.130	1	.000

The chi-square statistic is the difference in -2 log-likelihoods between the final model and a reduced model. The reduced model is formed by omitting an effect from the final model. The null hypothesis is that all parameters of that effect are 0.

a. This reduced model is equivalent to the final model because omitting the effect does not increase the degrees of freedom.

second-line treatment, or death from prostate cancer. A significant portion of men will have a detectable PSA level that plateaus and does not progressively rise.[15] Stephenson, et al. reviewed the Memorial Sloan Kettering experience of 3,125 patients who underwent RP. They found that after a median follow-up of 49 months, 75 men developed distant metastatic disease. Using a goodness-of-fit (R2) statistic, they examined 10 candidate definitions of PSA failure for their predictability of metastatic progression. They determined that a PSA value of at least 0.4 ng/mL followed by another increase was the best fit for metastatic progression, as well as high predictability for secondary therapy, continued PSA progression, and rapid doubling time.[16] In this study, 83.33% of those with detectable PSA had BCR while 16.67% did not progress to BCR. On the other hand, of those who had undetectable PSA, 95.83% did not progress to BCR.

Compared to a negative margin, men with positive margins in pT2 prostate cancer had a 12% increased risk for BCR, whereas in pT3a and pT3b, the increased risk was 12% and 18%, respectively. The length of positive margin also has been predictive of BCR, because those with margins greater than 1-3mm have a statistically significant increased risk for biochemical failure.[17,18,19] Others have found that multiple positive margins as well as location of margin may be prognostically significant.[8,19] In this study, the presence of PSM was found to be a predictor of BCR ($p < 0.001$). However, neither the length of the positive margin nor the presence of EPE at the margin was found to be predictors of BCR. A retrospective study by Kates, et al. in 2015 concluded that the histopathologic grade of the tumor at the PSM was correlated with increased risk of BCR.[18] In this study, GG of the tumor at the PSM was also found to be a predictor of BCR ($p = 0.008$).

Conclusion

Of the independent variables examined, clinical T stage, GG of RP specimen, presence of PSM, GG at positive margins, and detectable PSA were found to be significant predictors of BCR. Furthermore, multivariate analysis showed that only clinical T stage and detectable PSA after RP were independent predictors of BCR. Attentive assessment of these predictors in the preoperative period should aid the urologist in clinical decision-making and in advising patients regarding their prognosis.

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