Original Article

Biochemical failure after radical prostatectomy in intermediate-risk group men increases with the number of risk factors

Nobuki Furubayashi*, Takahito Negishi, Hidenori Iwai, Kei Nagase, Kenichi Taguchi[1], Mototsugu Shimokawa[2], Motonobu Nakamura

Departments of Urology and [1]Pathology, National Kyushu Cancer Center, [2]Institute for Clinical Research, National Kyushu Cancer Center, Fukuoka, Japan

*E-mail: furubayashi.n@nk-cc.go.jp

ABSTRACT

Introduction: We aimed to determine whether the number and type of risk factors are associated with biochemical recurrence-free survival after radical prostatectomy in men with D'Amico intermediate-risk prostate cancer.

Materials and Methods: Between August 1998 and May 2013, 481 Japanese patients underwent antegrade radical prostatectomy. The relationships between the rate of PSA failure after radical prostatectomy and the number and type of risk factors were examined in the intermediate-risk group.

Results: According to the D'Amico criteria, the low-, intermediate-, and high-risk groups comprised 107, 222, and 152 patients, respectively. The median follow-up period after surgery was 54.1 months. The 5-year PSA failure-free rates in the low-, intermediate-, and high-risk groups were 96.5%, 88.9%, and 72.6%, respectively ($P < 0.001$). The 5-year PSA failure-free rate in the intermediate-risk group with one, two, and three intermediate risk factors was 94.9%, 88.4%, and 49.0%, respectively ($P < 0.001$). The difference between the high- and intermediate-risk group with three intermediate risk factors was statistically significant based on the log-rank test ($P = 0.039$).

Conclusion: The number of intermediate risk factors is significantly associated with the PSA failure-free survival rate after radical prostatectomy in the intermediate-risk group. Patients classified into the intermediate-risk group based on all three intermediate risk factors are less likely to achieve a complete cure through surgery alone.

INTRODUCTION

The vast majority of men with prostate cancer will die of causes unrelated to their malignancy.[1-3] On the other hand, prostate cancer treatment is associated with complications and side effects, and affect the quality of life (QOL) after treatment. Hence, in determining the therapeutic strategies for prostate cancer, it is important to estimate the possibility of prostate cancer recurrence and survival. Risk classification and nomograms have been proposed as a method to evaluate the likelihood of prostate cancer recurrence and prognosis. Risk classification, such as the D'Amico classification.,[4] is a method of grouping patients with the same prognosis by combining multiple factors, such as the clinical tumor (cT) stage, prostate-specific antigen (PSA) level and Gleason score. According to the D'Amico criteria, the intermediate-risk group includes patients with three intermediate risk factors (clinical stage T2b lesions, a Gleason score of 7 or PSA level of >10 and ≤20 ng/ml). Cases that do not belong to the low- or high-risk groups are also assigned to the intermediate-risk group. As a result, the breadth of cases included in the intermediate-risk group is wide and the intermediate-risk group encompasses the largest population among the three groups in the D'Amico classification.[5,6] Therefore, more precise stratification and

Access this article online	
Quick Response Code:	Website: www.indianjurol.com
	DOI: 10.4103/0970-1591.194786

Received: 17.03.2016, **Accepted:** 06.09.2016

Financial support and sponsorship: Nil.

Conflicts of interest: There are no conflicts of interest.

personalized management might be required in patients classified in this group.[7] Although there is a variety of combination of factors, studies assessing factor combinations are limited. Therefore, the relationship between the PSA failure rates after RP (radical prostatectomy) and the number and conditions of intermediate risk factors were examined in the intermediate-risk group in the present study.

MATERIALS AND METHODS

Patient characteristics and risk group classification

Patients who underwent prostate biopsies and received a diagnosis of prostate cancer at the National Kyushu Cancer Center (Fukuoka, Japan) or additional associated institutions were assessed in this study. Embedded whole-mount antegrade open RP tissue specimens obtained from 638 patients with adenocarcinoma treated between August 1998 and May 2013 were reviewed. The patients underwent pelvic lymph node dissection during the same time period. A total of 157 patients were excluded from this study, including 151 patients due to a history of receiving hormonal therapy and six patients due to unclear biopsy or prostatectomy specimen findings. All patients were Japanese (median age, 66 years; range, 47–77), and the PSA levels ranged from 0.623 to 39.413 ng/ml (median, 7.491 ng/ml). The median follow-up period after surgery was 54.1 months.

The patients were classified into three risk groups according to the D'Amico criteria.[4] The low risk (stage T1c, T2a, and PSA level ≤10 ng/ml and Gleason score ≤6), intermediate risk (stage T2b or Gleason score of 7 or PSA level >10 and ≤20 ng/ml), and high risk (stage T2c or PSA level >20 ng/ml or Gleason score ≥8) groups comprised 107 (22.2%), 222 (46.2%), and 152 (31.6%) patients, respectively. The present study determined the cT classification based on only the results of the digital rectal exam, in accordance with the original study by D'Amico *et al*.[4] There are no patients who had been diagnosed posttransurethral prostatectomy. Since the risk classification of D'Amico is composed of three factors (cT stage, bGS7; biopsy Gleason score 7, and PSA > 10, ≤20), subanalyses according to the number and conditions of intermediate risk factors were additionally added. Two pathologists evaluated the grade of malignancy in the biopsy and prostatectomy specimens according to the 2005 International Society of Urological Pathology Consensus Conference on the Gleason grading system and determined the pathological stage based on the 2009 TNM classification.[8,9]

Methods

The RP specimens were fixed in 15% neutral buffered formalin (Wako Pure Chemical Industries, Ltd., Osaka, Japan) for 48 96 h, and whole organ prostate specimens were serially sectioned perpendicular to the rectal surface at 5 mm intervals. Sections that were predominantly caudal and cephalic were cut in the sagittal plane at 5 mm intervals to assess the bladder neck and apical margins. The specimens were subsequently embedded in paraffin, cut into 5 μm sections and stained with hematoxylin and eosin. Extraprostatic extension (EPE) was defined as an extension of the tumor from the prostate into the periprostatic soft tissue. The presence of tumor cells at the stained resection margin (RM) was defined as a positive RM. The follow-up schedule after RP involved a PSA assay performed every 3 months for the first 2 years, followed by every 4 months for the next 3 years and every 6 months thereafter. Disease recurrence and/or PSA failure were defined as the detection of a serum PSA level of >0.2 ng/ml or the use of RP if the PSA level did not decrease to below 0.2 ng/ml after surgery. A number of patients who underwent RP were subsequently treated with radiation and/or hormone therapy before the serum PSA level exceeded 0.2 ng/ml. Therefore, in these patients, the time point of adjuvant therapy was defined as the date of disease recurrence. All patients provided their written informed consent to participate in this study, and the study protocol was approved by the ethics committee of the National Kyushu Cancer Center.

Statistical analysis

The statistical analyses were carried out using the JMP® Pro, Version 11.0.0 software package (SAS Institute, Inc., Cary, NC, USA). The PSA failure-free rate was determined according to the Kaplan–Meier method, and the significance of clinicopathological parameters associated with PSA failure was assessed using the Cox proportional hazards regression model. The log-rank test and Kruskal–Wallis test were used to determine differences between the risk groups and groups of each number of risk factors. $P < 0.05$ was considered to indicate a statistically significant difference.

RESULTS

Clinicopathological characteristics according to risk group [Table 1]

No differences were observed in the age of the patients between the groups. Based on the RP Gleason score, the low-, intermediate-, and high-risk groups had high-grade (Gleason score ≥8) tumors in 9.3% (10/107), 15.3% (34/222), and 42.1% (64/152) of the patients, respectively. The pathological stage was ≥T3 in 17.8% (19/107), 35.1% (78/222), and 54.0% (82/152) of patients in the low-, intermediate-, and high-risk groups, respectively. Lymph node involvement was observed in 1, 5 and 7 patients in the low-, intermediate-, and high-risk groups, respectively.

Correlations between patient characteristics and PSA failure [Table 2]

The 5-year PSA failure-free rate in the low-, intermediate-, and high-risk groups was 96.5%, 88.9%, and 72.6%, respectively [Figure 1]. The difference between the low and intermediate-risk groups and between the intermediate

Table 1: Clinico-pathological characteristics based on risk groups

Risk group	Low	Intermediate	High
Total number of patients	107	222	152
Median age (range)	66 (47-77)	66 (57-76)	67 (48-77)
Clinical stage (%)			
cT1c	84 (78.5)	157 (70.7)	77 (50.7)
cT2a/b	23 (21.5)	65 (29.3)	47 (30.9)
cT2c	-	-	21 (13.8)
cT3	-	-	7 (4.6)
Preoperative PSA (%)			
≤10	107 (100)	151 (68.1)	83 (54.6)
>10, ≤20	-	71 (31.9)	36 (23.7)
>20	-	-	33 (21.7)
Biopsy Gleason score (%)			
≤6	107 (100)	19 (8.6)	8 (5.2)
7	-	203 (91.4)	27 (17.8)
≥8	-	-	117 (77.0)
RP Gleason score (%)			
≤6	45 (42.1)	18 (8.2)	6 (3.4)
7	52 (48.6)	170 (76.5)	82 (53.9)
≥8	10 (9.3)	34 (15.3)	64 (42.1)
Pathological stage (%)			
pT2a/b	18 (16.8)	27 (12.2)	9 (5.9)
pT2c	70 (65.4)	117 (52.7)	61 (40.1)
pT3a	17 (15.9)	71 (32.0)	64 (42.1)
pT3b	2 (1.9)	7 (3.1)	18 (11.9)
EPE	17 (15.9)	66 (29.7)	65 (42.8)
RM	13 (12.1)	45 20.3)	35 (23.0)
sv	2 (1.9)	7 (3.2)	18 (11.8)
pN	1 (0.9)	5 (2.3)	7 (4.6)

Clinical and pathological staging was based on the TNM classification (2009). cT=Clinical tumor stage, PSA=Prostatespecific antigen, RP=Radical prostatectomy, pT=Pathological tumor stage, EPE=Extraprostatic extension, RM=Resection margin, sv=Seminal vesicle invasion, pN=Pathological lymph node metastasis $P<0.05$ was considered to indicate a statistically significant difference

Table 2: Correlation between patient characteristics and PSA failure

Variable	Hazard ratio	*P*	95%CI
Univariate analysis			
Age, <70 vs. ≥70	1.180	0.705	0.518-3.022
PSA, >0, ≤10 vs. >10, ≤20	1.625	0.242	0.709-3.551
cT1c vs. cT2a/b	10.274	<0.001	4.350-28.227
RP Gleason score, ≤7 vs. ≥8	3.188	0.010	1.354-7.020
pT2 vs. pT3	3.627	0.001	1.653-8.516
EPE absent vs. present	3.240	0.003	1.470-7.240
RM absent vs. present	1.198	0.703	0.438-2.816
SV absent vs. present	6.378	0.006	1.834-17.017
pN absent vs. present	18.860	<0.001	4.207-62.156
Multivariate analysis			
Age, <70 vs. ≥70	1.655	0.245	0.718-4.279
PSA, >0, ≤10 vs. >10, ≤20	1.237	0.636	0.494-2.872
cT1c vs. cT2a/b	11.481	<0.001	4.754-32.310
RP Gleason score, ≤7 vs. ≥8	1.728	0.237	0.684-4.074
pT2 vs. pT3	2.349	0.068	1.001-5.717
EPE absent vs. present	2.252	0.061	1.033-5.063
RM absent vs. present	1.614	0.334	0.581-3.875
SV absent vs. present	8.538	0.003	2.383-24.473
pN absent vs. present	2.914	0.199	0.529-12.559

Clinical and pathological staging was based on the TNM classification (2009). PSA=Prostatespecific antigen, cT=Clinical tumor stage, RP=Radical prostatectomy, pT=Pathological tumor stage, EPE=Extraprostatic extension, RM=Resection margin, SV=Seminal vesicle invasion, pN=Pathological lymph node metastasis, CI=Confidence interval $P<0.05$ was considered to indicate a statistically significant difference

and high-risk groups was statistically significant ($P = 0.011$ and $P < 0.001$ respectively). In the multivariate analysis, statistically significant differences were found in the T stage and seminal vesicle invasion among the patients with and without PSA failure [Figure 1].

According to the Cox proportional hazards analysis of the intermediate-risk group, among the preoperative variables, only the T stage was a significant predictor. Meanwhile, postoperative characteristics, such as the RP Gleason score, pathological tumor stage, EPE, seminal vesicle invasion, and positive lymph nodes were significant predictors based on a univariate analysis.

PSA failure rates based on number and nature of intermediate risk factors [Table 3]

122 cases (55.0%) had only 1 intermediate-risk factor, among which PSA failure was noted in four cases (3.3%). Of these, 108 cases (48.7%) were so classified due to GS7 only and all PSA failure cases were in this group.

83 cases (37.4%) had two intermediate risk factors, among which PSA failure was noted in 14 cases (16.9%). 43 of these (19.4%) had cT2a/b and GS7 as the risk factors and PSA failure occurred in 12 of them (27.9%). 35 cases (15.8%) had GS7 and PSA between 10-20ng/ml as the risk factors and PSA failure occurred in two cases (5.7%).

Only 17 cases (7.7%) had all three intermediate risk factors, and PSA failure was noted in eight of these cases (47.1%).

PSA failure rate increased as the number of intermediate risk factors increased, and there was a significant difference among groups based on the total number of risk factors ($P < 0.001$). The 5-year PSA failure-free rate in the one, two and three intermediate risk factor groups was 94.9%, 88.4%, and 49.0%, respectively [Figure 2]. The difference between the one and two intermediate risk factor

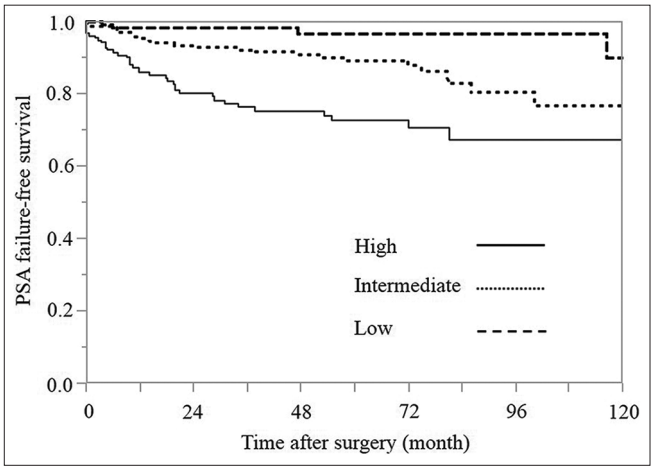

Figure 1: Kaplan–Meier estimates of PSA failure free survival according to the risk group ($P < 0.001$; df = 2). PSA = Prostate specific antigen

Table 3: PSA failure rates based on number and nature of intermediate risk factors

No. of risk factors	Individual factors	Patients (*n*) (%)	PSA failures (*n*) (%)	*P*
One		122 (55.0)	4 (3.3)	<0.001
Two		83 (37.4)	14 (16.9)	
Three		17 (7.6)	8 (47.1)	
One				
	cT2a/b	0	0	0.466
	PSA 10-20 ng/ml	14 (6.3)	0	
	bGS7	108 (48.7)	4 (3.7)	
Two				
	cT2a/b + PSA 10-20 ng/ml	5 (2.2)	0	0.021
	bGS7 + PSA 10-20 ng/ml	35 (15.8)	2(5.7)	
	cT2a/b + bGS7	43 (19.4)	12 (27.9)	
Three				
	cT2a/b + bGS7 + PSA 10-20 ng/ml	17 (7.6)	8(47.1)	

Clinical and pathological staging was based on the TNM classification (2009). PSA=Prostatespecific antigen, cT=Clinical tumor stage, bG=Biopsy Gleason score, $P<0.05$ was considered to indicate a statistically significant difference

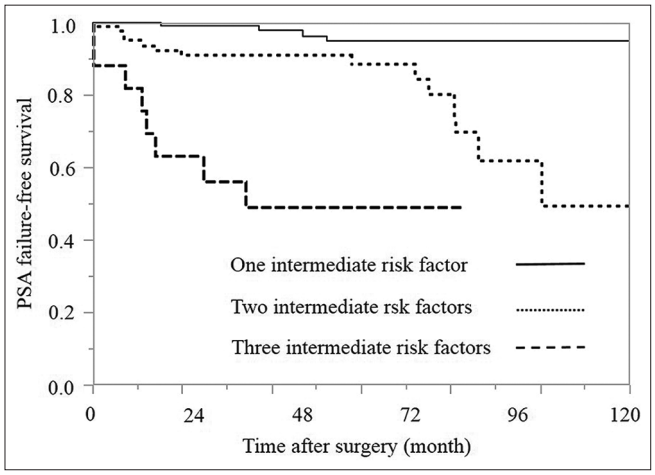

Figure 2: Kaplan–Meier estimates of PSA failure free survival according to the number of factors ($P < 0.001$; df = 2). PSA = Prostate specific antigen

groups was statistically significant according to the log-rank test ($P < 0.001$). In addition, the difference between the one and three intermediate risk factor groups was statistically significant based on the log-rank test ($P < 0.001$). The difference between the two and three intermediate risk factor groups was also statistically significant according to the log-rank ($P < 0.001$).

DISCUSSION

This study analyzed men with intermediate-risk prostate cancer according to the D'Amico criteria and sought to determine whether the number and type of intermediate risk factors are associated with the PSA failure-free survival rate after RP.[4] Our results provide evidence to support the hypothesis that a greater number of intermediate risk factors is associated with an increased risk of PSA failure after RP in the intermediate-risk group and that cases classified into the intermediate-risk group based on all three intermediate risk factors are believed to include patients less likely to achieve a complete cure through surgery alone.

The results showed that the rate of a PSA failure-free rate in relation to the follow-up timeline achieved with RP alone in the intermediate-risk group was significantly lower than that observed in the low-risk group ($P = 0.011$), and significantly higher than that observed in the high-risk group ($P < 0.001$). In addition, the correlations between the characteristics and PSA failure were examined in the intermediate-risk group [Table 2]. According to the results of the multivariate analysis, of the preoperative variables, the cT stage was a significant predictor in the patients with and without PSA failure ($P < 0.001$). In addition, there were no cases of PSA failure among the bGS6 cases. Therefore, the preoperative variable of the biopsy Gleason score was not analyzed in the Cox proportional hazards regression model. Furthermore, the univariate and multivariate analyses did not reveal any statistically significant differences in the preoperative variables, including the preoperative PSA level, which is a component of the risk profile in the D'Amico risk classification ($P = 0.242$). However, the intermediate-risk group included only cases that did not belong to the low- or high-risk groups, and a potential problem with the risk classification system is the heterogeneity of patients in the intermediate risk category who have a different number of risk group determinants. Hence, the breadth of cases included in the intermediate-risk group was unexpectedly wide. Therefore, additional analyses were carried out with the intermediate risk factors used for risk stratification, including the PSA level, bGS, and cT status, in the intermediate-risk group.

First, the number and breakdown of intermediate risk factors were analyzed in the intermediate-risk group. As demonstrated in Table 3, 122 cases (55.0%) was classified into the intermediate-risk group based only on one intermediate

risk factor, while 83 cases (37.4%) were classified according to two intermediate risk factors. Only 17 cases (7.7%) were classified based on all three intermediate risk factors; however, PSA failure was noted in eight cases (47.1%) at high rates. The PSA failure rate also increased as the number of intermediate risk factors increased, and there was a significant difference among the risk factor number groups ($P < 0.001$). Furthermore, in the two intermediate risk factors group, there was a significant difference in the condition, cT2a/b+bGS7 ($P = 0.021$).

An analysis of the PSA failure-free survival rate in each risk factor number group was subsequently performed. The 5-year PSA failure-free rate in the one, two and three intermediate risk factor groups was 94.9%, 88.4%, and 49.0%, respectively [Figure 2]. The difference between the one and two intermediate risk factor groups was statistically significant according to the log-rank test ($P < 0.001$), while the difference between the one and three intermediate risk factor groups was statistically significant based on the log-rank test ($P < 0.001$). Judging from these results, as the number of the intermediate risk factors increases, cases classified into the intermediate-risk group are believed to have a higher rate of PSA failure through surgery alone. In addition, the 5-year PSA failure-free rate in the low-risk group and intermediate-risk group with one intermediate risk factor was 96.5% and 94.9%, respectively, and the difference between these two groups was not statistically significant according to the log-rank test ($P = 0.729$). On the other hand, the 5-year PSA failure-free rate in high-risk group and intermediate-risk group with three intermediate risk factors was 72.6% and 49.0%, respectively, and the difference between these two groups was statistically significant according to the log-rank test ($P = 0.039$). Several studies have demonstrated the merit of the idea that males with multiple intermediate risk factors have similar outcomes as those with high-risk disease.[10,11] However, in the current study, the 5-year PSA failure-free rate of the cases classified into the intermediate-risk group based on all three intermediate risk factors was significantly lower than that seen in the high-risk group. The intermediate-risk group with all three intermediate risk factors is believed to comprise patients less likely to achieve a complete cure via surgery alone. Recent studies suggest that men with three or four of the unfavorable risk factors, including an elevated PSA velocity, and treated with either external beam radiotherapy or prostatectomy, are at particularly high risk of death from prostate cancer.[10,12] These cases might also require additional treatment strategies in the early postoperative period or novel therapies, to improve the potentially poor prognosis. In addition, the risk factors considered in the present study were pretreatment clinical risk factors, and many reported pathological risk factors of PSA failure after RP (including the pathological tumor stage, Gleason score, EPE, seminal vesicle invasion, positive surgical, margins, and others) are thought to possibly be better prognostic indicators.[13-15] Therefore, the number of risk factors construct, as presented in this study, is most useful for counseling and decision-making in the pretreatment setting.

CONCLUSION

The number of intermediate risk factors is significantly associated with the PSA failure-free survival rate after RP in the intermediate-risk group. Men with one risk factor only are more likely to achieve a complete cure via surgery alone, whereas men with all three risk factors are less likely to achieve a complete cure with surgery alone.

REFERENCES

1. Ganz PA, Barry JM, Burke W, Col NF, Corso PS, Dodson E, *et al*. National Institutes of Health State-of-the-Science Conference: Role of active surveillance in the management of men with localized prostate cancer. Ann Intern Med 2012;156:591-5.
2. Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, Fox S, *et al*. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med 2012;367:203-13.
3. Stattin P, Holmberg E, Johansson JE, Holmberg L, Adolfsson J, Hugosson J; National prostate cancer register (NPCR) of Sweden. Outcomes in localized prostate cancer: National prostate cancer register of Sweden follow-up study. J Natl Cancer Inst 2010;102:950-8.
4. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, *et al*. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 1998;280:969-74.
5. Zumsteg ZS, Spratt DE, Pei I, Zhang Z, Yamada Y, Kollmeier M, *et al*. A new risk classification system for therapeutic decision making with intermediate-risk prostate cancer patients undergoing dose-escalated external-beam radiation therapy. Eur Urol 2013;64:895-902.
6. Corcoran NM, Hovens CM, Metcalfe C, Hong MK, Pedersen J, Casey RG, *et al*. Positive surgical margins are a risk factor for significant biochemical recurrence only in intermediate-risk disease. BJU Int 2012;110:821-7.
7. D'Amico AV. Personalizing the management of men with intermediate-risk prostate cancer. Eur Urol 2013;64:903-4.
8. Epstein JI, Allsbrook WC Jr., Amin MB, Egevad LL; ISUP Grading Committee. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason grading of prostatic carcinoma. Am J Surg Pathol 2005;29:1228-42.
9. James D. Brierley, Mary K. Gospodarowicz, Christian Wittekind. TNM Classification of Malignant Tumors. 7th ed. Oxford: Wiley-Blackwell; 2009.
10. Nguyen PL, Chen MH, Catalona WJ, Moul JW, Sun L, D'Amico AV. Predicting prostate cancer mortality among men with intermediate to high-risk disease and multiple unfavorable risk factors. Int J Radiat Oncol Biol Phys 2009;73:659-64.
11. Zelefsky MJ, Leibel SA, Gaudin PB, Kutcher GJ, Fleshner NE, Venkatramen ES, *et al*. Dose escalation with three-dimensional conformal radiation therapy affects the outcome in prostate cancer. Int J Radiat Oncol Biol Phys 1998;41:491-500.
12. D'Amico AV, Chen MH, Catalona WJ, Sun L, Roehl KA, Moul JW. Prostate cancer-specific mortality after radical prostatectomy or external beam radiation therapy in men with 1 or more high-risk factors. Cancer 2007;110:56-61.
13. Blute ML, Bergstralh EJ, Iocca A, Scherer B, Zincke H. Use of Gleason score, prostate specific antigen, seminal vesicle and margin status

to predict biochemical failure after radical prostatectomy. J Urol 2001;165:119-25.
14. Freedland SJ, Aronson WJ, Terris MK, Kane CJ, Amling CL, Dorey F, *et al*. Percent of prostate needle biopsy cores with cancer is significant independent predictor of prostate specific antigen recurrence following radical prostatectomy: Results from Search database. J Urol 2003;169:2136-41.
15. Gretzer MB, Epstein JI, Pound CR, Walsh PC, Partin AW. Substratification of stage T1C prostate cancer based on the probability of biochemical recurrence. Urology 2002;60:1034-9.

How to cite this article: Furubayashi N, Negishi T, Iwai H, Nagase K, Taguchi K, Shimokawa M, *et al*. Biochemical failure after radical prostatectomy in intermediate-risk group men increases with the number of risk factors. Indian J Urol 2017;33:64-9.