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Abstract

Purpose

The Grade Group (GG) classification is recommended by guidelines as a reliable prognostic factor of prostate cancer. However, most studies have been performed on the Caucasian population.

Our objective was to validate GG classification as a safe way to classify intermediate- and high-risk patients with African ancestry.

Patients and methods

This was a retrospective study in an Afro-Caribbean population. A total of 1,236 patients were included between 2000 and 2015. Patients were stratified according to (GG). Survival analysis was performed using the Kaplan Meier method, univariate and multivariate analyses using the Cox model.

Results

There was no significant difference at five and ten-year BCR-free survival between the intermediate- and high-risk groups, based on the D'Amico classification. There was a highly significant difference in BCR-free survival at five ($p < 0.0001$) and ten years ($p < 0.0001$) for patients of GG 1 and 2 versus 3, 4, and 5, respectively. There was no significant difference in five-year BCR-free survival of patients of GG grades 1 and 2, whether lymph node dissection was performed or not. There was a significant difference between GG 2 and 3 patients in five ($p = 0.008$) and ten-year BCR-free survival ($p = 0.01$). High PSA ($p < 0.0001$), pathological

GG ≥ 3 ($p < 0.0001$), pathological stage pT3 ($p < 0.0001$) and positive margins ($p < 0.0001$) were factors for BCR in multivariate analysis.

Conclusion

The GG 2015 classification appears to be a better prognostic factor than D'Amico classification for intermediate- and high-risk Afro-Caribbean patients.

Key words: prostate cancer, biochemical recurrence, Afro-Caribbean, ISUP classification, Grade Group

Introduction

Prostate cancer (Pca) is the most common cause of non-cutaneous cancer among men worldwide and the leading cause among men in developed countries [1]. There are guidelines to optimize the treatment of localized prostate cancer. They were developed using classifications and/or nomograms to provide the best prediction for the risk of disease recurrence based on tumor characteristics and aggressiveness at diagnosis.

One of the historical classifications is that of D'Amico, based on digital rectal examination (DRE), PSA, and biopsy Gleason Score [2]. Some Guidelines suggest using nomograms, such as Briganti or Partin tables, to evaluate the risk of biochemical recurrence (BCR) or lymph-node invasion [3, 4]. Since the IUSP 2014 and Grade Group (GG) 2015 classification, based on the Gleason biopsy score, has been used and integrated into several guidelines as a reliable classification criterion to predict the risk of recurrence [5, 6, 7]. However, most studies of the GG classification are not on subjects of African descent. Similarly, most nomograms or validated classification systems, such as that of D'Amico, have been developed using data from mostly Caucasian patients. Such tools have been externally validated in many cohorts of Caucasian populations or those of mixed ethnicity, but less in cohorts consisting exclusively of men of African ancestry [8].

Our objective was to validate Grade Group 2015 as a reliable method to classify patients with African ancestry according to risk group, in particular for intermediate- and high-risk patients.

Patients and Methods

Study population

This was a retrospective study of prostate cancer patients undergoing radical prostatectomy (RP) at the University Hospital of Guadeloupe, corresponding to approximately 60% of new cases in the country. Guadeloupe is a French Caribbean archipelago of 410,000 inhabitants where most of the population (~90%) is of African ancestry. A total of 1,236 patients were included between January 1, 2000 and December 31, 2015, of which 126 were excluded due to missing data and 10 because they were treated with neoadjuvant hormonal therapy or radiotherapy. Only patients classified as having intermediate- or high-risk localized prostate cancer before surgery with pre-operative data as digital rectal examination, PSA and biopsy Gleason score, according to the D'Amico classification, were considered. After surgery, all patients were followed by serial PSA determinations and clinical visits every six months for the first three years and annually thereafter. BCR was defined as two consecutive (usually four weeks apart) PSA measurements above 0.2 ng/ml.

Data collection

For each patient, we collected data on their age at positive biopsy and surgery, the preoperative PSA value, clinical stage, biopsy Gleason score, date of surgery, type of surgery, perioperative blood loss (as recorded in the operative notes), pathological clinical stage, pathological Gleason score, surgical margins, lymphadenectomy status, prostate weight, and follow-up PSA. Patients were stratified according to GG (1 to 5). Firstly, GG 1 and 2 (respectively, Gleason score 6 and 7 (3 + 4)) were grouped. Secondly, we grouped GG 3, 4, and 5 (respectively, Gleason score 7 (4 + 3), 8 and 9-10).

Only the medical data from the database of all radical prostatectomies performed in our department was used. The study was approved by the Ethics Committee of the University Hospital of Pointe-à-Pitre.

Statistical analysis

GG were stratified into two groups: GG 1 and 2 *versus* GG 3, 4, and 5. Five- and ten-year BCR-free survival rates were calculated by Kaplan-Meier analysis. Kaplan-Meier survival curves were stratified into intermediate- and high-risk groups according to the D'Amico classification or the ISUP Score in two groups and paired log-rank tests were performed. These analyses were restricted to patients with a follow-up of at least 10 years. Five- and ten-year BCR-free survival rates were additionally calculated by the Kaplan-Meier method to compare GG 2 and GG 3.

The free survival rate without salvage radiotherapy was calculated by Kaplan-Meier analyses.

Five-year BCR-free survival rates were estimated by Kaplan-Meier analysis for patients who had a lymphadenectomy or not.

The hazard ratio (HR) and 95% confidence intervals (CI) for the association between individual characteristics and BCR were estimated using the *Cox proportional-hazards regression* model for univariate and multivariate analyses. Only significant variables in univariate model were included in multivariate model. Time to event was defined as the duration between the date of surgery and the PSA value that defined the recurrence event. Patients who did not relapse were censored at the last normal post-operative PSA measurement before December 31, 2017.

All analyses were carried out using StatView version 5.0 and MedCalc version 17.5 software. All tests were two-tailed, and P values < 0.05 were considered to be statistically significant.

Results

A total of 1,100 patients classified in the intermediate- or high-risk groups of D'Amico were included. The median age at diagnosis was 65 years (44 – 77). The median PSA was 9.3 ng/ml (0.84 – 66). The rate of positive margins was 31.7%. A total of 306 patients (29%) had biochemical recurrence and 253 (23%) received salvage treatment. The median time between surgery and salvage treatment was 2.3 years. The median time to follow up was six years. Baseline characteristics of all patients are summarized in Table 1.

There were no significant differences in five- (HR = 0.97, 95% CI [0.66 – 1.44], p = 0.89) or ten-year BCR-free survival (HR = 1.01, 95% CI [0.72 – 1.43] p = 0.94 (Figure 1a and 1b) for the intermediate- and high-risk groups, based on the D'Amico classification. The results were similar for survival without salvage treatment.

Stratification of the population based on ISUP groups showed there to be a highly significant difference in BCR-free survival without biochemical recurrence at five (HR = 1.77; 95% CI [1.32 – 2.37], p < 0.0001) and ten years (HR = 1.64, 95% CI [1.26 – 2.14], p < 0.0001) (Figure 2a and 2b). Similarly, the time to salvage treatment was longer for the group of patients with ISUP scores of 3, 4, or 5 than those with ISUP grade 1 or 2 (HR = 1.42, 95% CI [1.05 – 1.91], p = 0.01) (Figure 3).

There was no significant difference in five-year BCR-free survival of the patient group with ISUP scores of 1 or 2, whether lymph node dissection was performed or not (HR = 1.07, 95% CI [0.75 – 1.62], p = 0.75) (Figure 4).

However, there was a significant difference between patients with ISUP scores of 2 and 3 for five- (HR = 1.55 ; 95% CI [1.10 – 2.17], p = 0.008) and ten-year BCR-free survival (HR = 1.45, 95% CI [1.07 – 1.96], p = 0.01) (Figure 5a and 5b).

In univariate analysis, predictive factors associated with biochemical recurrence were PSA, the biopsy Grade Group, the pathological Grade Group, the pathological stage (pT3 stage: pT3a and b), the surgical margins and the lymphadenectomy (Table 2). High PSA ($p < 0.0001$), Grade Group ≥ 3 for prostate specimen ($p < 0.0001$), extra-capsular prostatic involvement (pT3a), and/or seminal-vesicle invasion (pT3b) ($p < 0.0001$) and positive margins ($p < 0.0001$) were factors for biochemical recurrence in multivariate analysis (Table 3). Similarly, in univariate analysis, PSA, abnormal clinical stage, Grade Group ≥ 3 for biopsy and prostate specimen, pathological stage, and surgical margins were risk factors associated with catch-up treatment (Table 4). Thus, high PSA ($p = 0.005$), a pathological Grade Group ≥ 3 ($p = 0.001$), the pathological stage (pT3 stage: pT3a and b) ($p = 0.0006$) and the presence of positive surgical margins ($p = 0.002$) were risk factors for performing salvage treatment in multivariate analysis (Table 5).

Discussion

Our main finding was a better stratification of patients according to their risk groups using the Grade group rather than the D'Amico classification. Patients with Grade Group of 1 or 2 showed significantly higher BCR-free survival and better disease-free survival without salvage treatment after RP than patients with Grade Group of 3, 4, or 5. There was no benefit in performing a lymphadenectomy for patients with Grade Group of 1 or 2. In multivariate analysis, the biopsy Gleason score appeared to more efficiently predict BCR and disease-free survival without salvage treatment. Our results suggest that the D'Amico classification is not the best classification to distinguish between intermediate- and high-risk patients of African ancestry. In a previous study with 964 Afro-Caribbean men, we found similar results. According to D'Amico classification, five-year BCR-free survival Kaplan-Meier curves stratified into low, intermediate and high risk were significant between low- and intermediate-

risk ($p < 0.001$) and low- and high-risk patients ($p < 0.001$) but non-significant between intermediate- and high-risk men ($p = 0.67$) [9].

There are several possible explanations for our findings. The D'Amico classification is based on DRE, biopsy Gleason score, and PSA. DRE is not reproducible between physicians. PSA levels may vary depending on prostate volume, the presence of prostate cancer, or infection. However, the PSA test has a positive predictive value of 25 to 35% for a PSA level between 4 and 10 and a positive predictive value of 50 to 80% for a PSA level > 10 [10]. Several studies claim racial disparities in PSA levels, with a higher level for black men or a much more rapid increase in PSA level over time in African-American than Caucasian men [11, 12, 13]. Some studies have reported a higher Gleason score for the Black population than for Caucasian men [12, 14]. The Gleason score using Grade Group may be a better criterion at diagnosis than DRE and PSA.

The classification of patients by pathologists using the Gleason score was modified in 2005. However, Lucia *et al.* showed similar score distributions between the classic and modified Gleason scoring systems [15]. A new ISUP classification system was created in 2014 and is now integrated into current guidelines [6]. According to Grogan *et al.*, the ISUP 2014 grading system is a significant independent predictor of both biochemical recurrence and clinical recurrence after RP [16]. It is clear that Gleason 7 (3 + 4) and (4 + 3) patients do not have the same risk of recurrence and that it is important to distinguish between them to make the best estimate of the prognosis [17, 18].

This study is one of the largest in terms of the number of included patients with African ancestry. Our results suggest that ISUP 2014 or Grade Group can be used safely to provide the best overall prognosis of the risk of BCR in this population, particularly for intermediate- and

high-risk patients. Our results also suggest that lymphadenectomy does not improve BCR in GG 1 and GG 2 patients.

In addition, Schulman et al. using the SEARCH database including 1002 African American men suggested an independent clinical utility of the Grade Group on biopsy as a reliable prognostic factor for BCR after radical prostatectomy [19].

The limits of this study were its retrospective nature and the limited number of lymphadenectomies performed.

There are many nomograms for predicting BCR or the probability of lymph-node involvement, but they were all developed using data from predominantly Caucasian populations. Bandini *et al.* performed a validation and head-to-head comparison of four nomograms (the Cagiannos, the 2012-Briganti, the Godoy, and the online-Memorial Sloan Kettering Cancer Center (MSKCC) for the prediction of lymph-node invasion in African Americans. All C-index values were lower in Afro Americans than Caucasians: Cagiannos (76.1 *vs* 79.5%), Godoy (73.0 *vs* 79.4%), 2012-Briganti (73.3 *vs* 81.3%), and MSKCC (72.6 *vs* 81.6%). He concluded that the Cagiannos nomogram should be favored for African Americans, with only 2,668 black men *versus* 14,077 Caucasians included in this study [20].

In conclusion, the Grade Group 2015 classification appears to be a better prognostic factor for intermediate- and high-risk Afro-Caribbean patients than D'Amico classification.

We will next develop a nomogram based on patients of mostly African descent.

Words account: 1931

Authors' Contribution

E Perrot: Project development, Data collection, Manuscript writing.

S Seddik: Data collection

G Gourtaud: Manuscript editing

R Eyraud: Manuscript editing

V Roux: Manuscript editing

C Moureaux: Data collection

P Blanchet: Project development.

L Brureau: Project development, Data analysis, Manuscript writing.

Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflict of interest.

Research involving human participants and/or animals

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

This is a retrospective study. For this type of study formal consent is not required.

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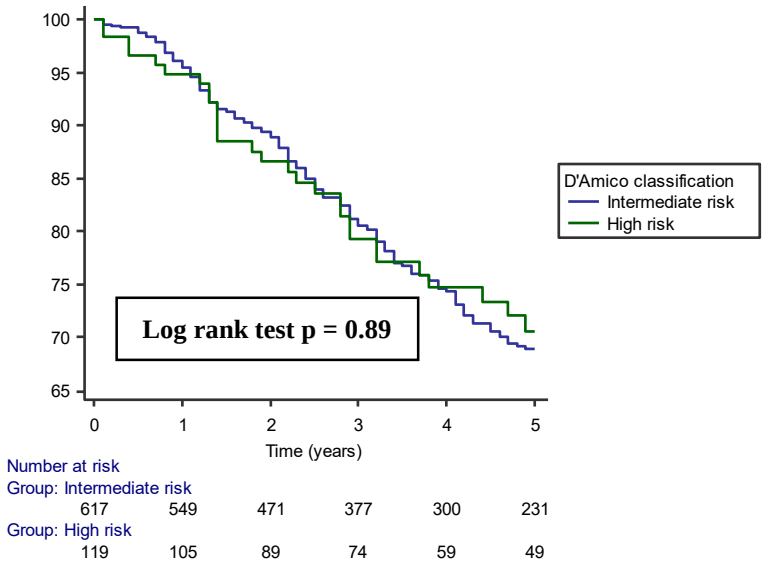
a.



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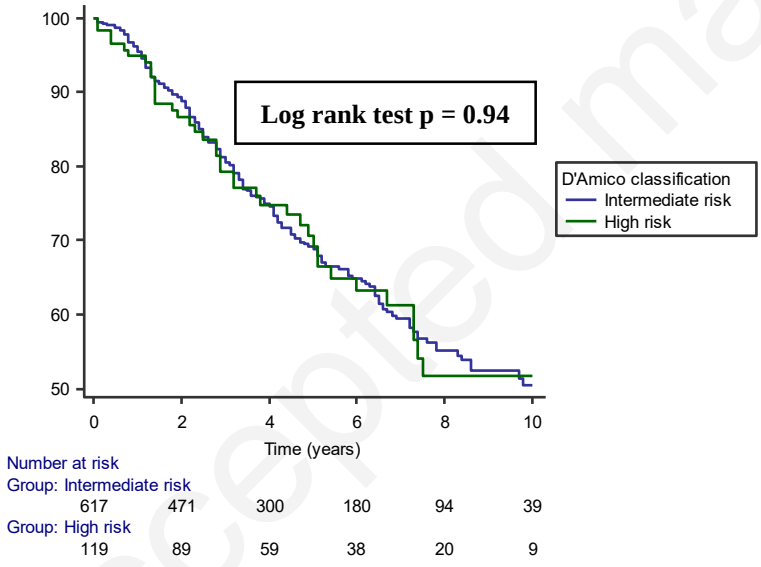
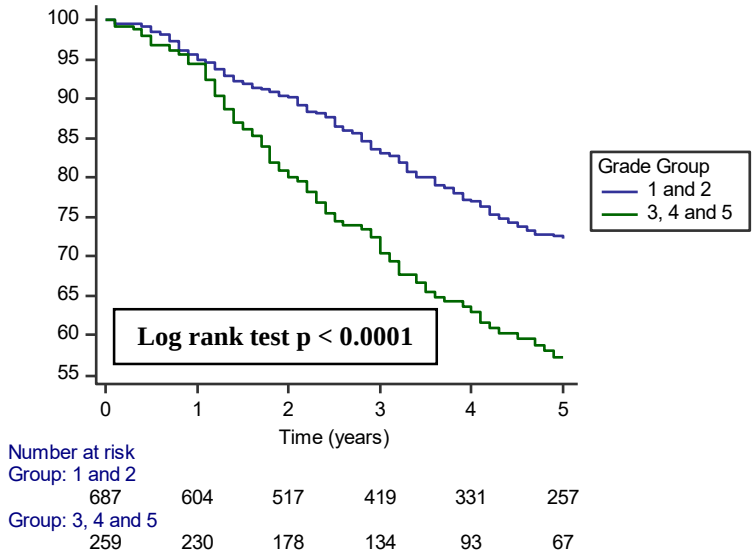


Figure 1. Five- and ten-year BCR-free survival according to the D'Amico classification.

a.



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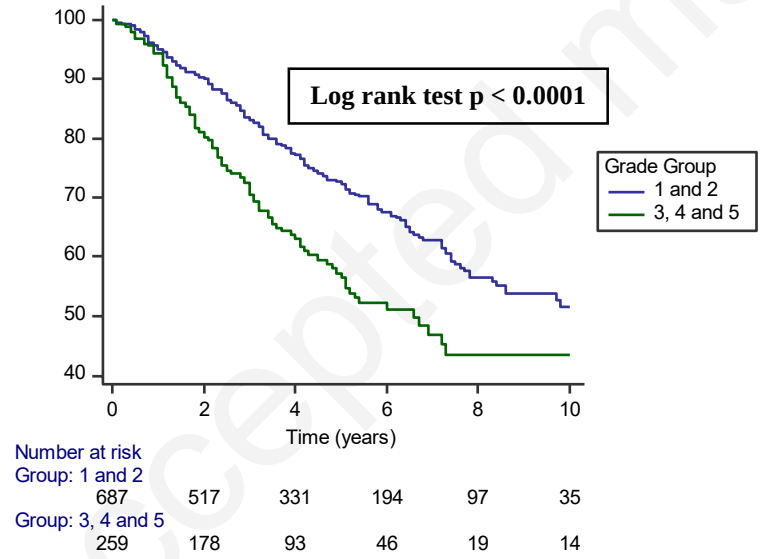


Figure 2. Five and 10-year BCR-free survival according to Grade Group.

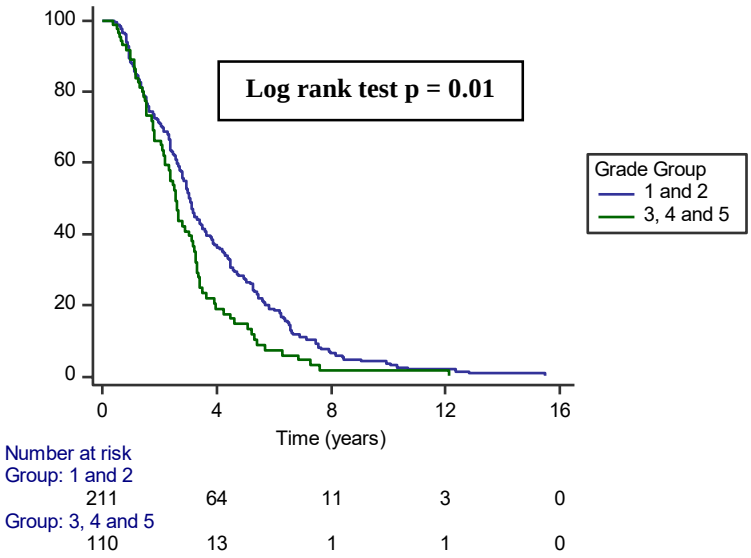


Figure 3. Free survival without salvage treatment according to Grade Group.

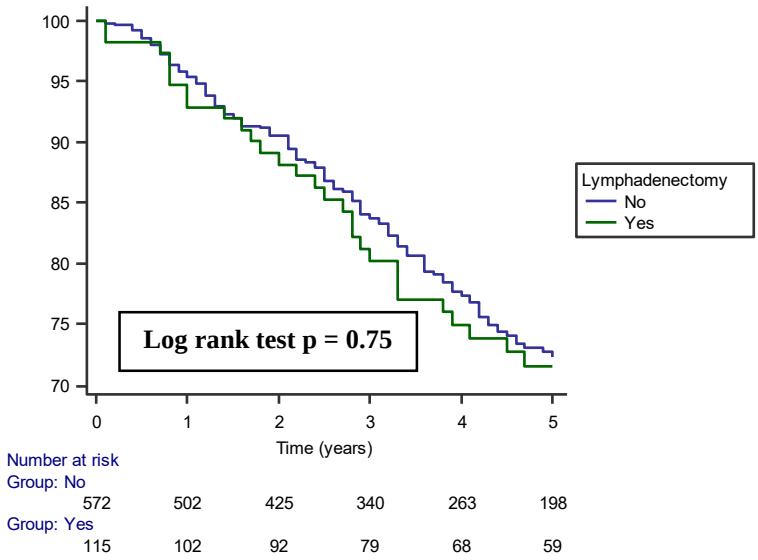
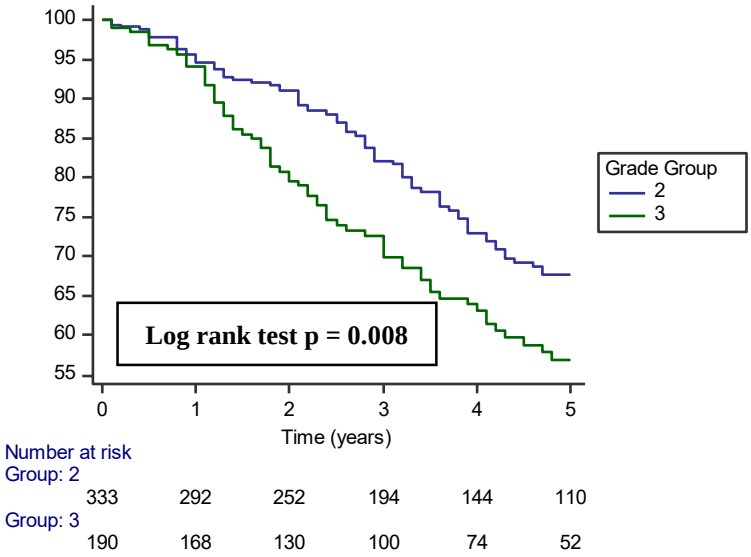


Figure 4. Five-year BCR-free survival for Grade Group 1 and 2 patients according to lymphadenectomy status.

a.



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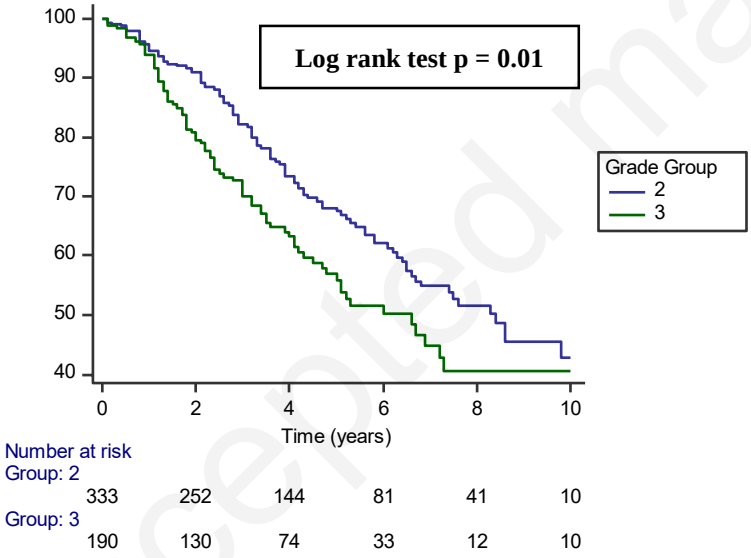

Figure 5. Five- and 10-year BCR-free survival according to Grade Group 2 and 3.

Table 1. Baseline patient characteristics

VARIABLES	TOTAL
Number of patients (%)	1100 (100%)
	Median (range)
Age at diagnosis (years)	65 (44 – 77)
PSA at diagnosis (ng/mL)	9.3 (0.84 – 66)
Follow up (years)	6.0 (0.11 – 15.0)
Time to salvage treatment (years)	2.3 (0.1 – 15.0)
	N (%)
Clinical stage T1-T2 T3	 1095 (99.5) 5 (0.5)
Biopsy Grade Group: 1 (≤ 6) 2 (3+4) 3 (4+3) 4 (8) 5 (9-10)	 399 (36.3) 384 (34.9) 229 (20.8) 83 (7.5) 5 (0.5)
D'Amico classification* - intermediate risk - high risk	 696 (82.8) 145 (17.2)
Prostate specimen: - Gleason score/ Grade Group (GG): ≤ 6 = GG 1 7 = GG 2 / GG 3 ≥ 8 = GG 4 / GG 5 - Pathological stage pT2 pT3 – pT4 - Extracapsular extension (pT3a): No Yes - Seminal invasion (pT3b): No Yes - Positive margins: No Yes	 273 (24.8) 741 (67.4) = 510 / 231 86 (7.8) = 61 / 25 824 (74.9) 276 (25.1) 972 (88.4) 128 (11.6) 958 (87.1) 142 (12.9) 751 (68.3) 349 (31.7)
Lymphadenectomy: No: Nx Yes : total / N0 / N1	 859 (78.1) 241 (21.9) / 220 / 21
Biochemical recurrence** No Yes Early recurrence	 641 (60.8) 306 (29.0) 108 (10.2)
Salvage treatment No Yes	 847 (77.0) 253 (23.0)

*Intermediate- or high-risk status could not be defined for 259 patients due to missing data for one of the criteria but there are at least one criteria to classify in intermediate- or high-risk group.

**The biochemical recurrence status was not known for 45 patients

Table 2. Univariate analyses of BCR risk factors

Variables	**HR**	**95% CI**	***P* value**
Pre-operative data			
Age (years)	1.01	0.99 – 1.03	0.13
PSA (ng/ml)	**1.04**	**1.03 – 1.06**	**< 0.001**
Clinical stage			
T1 – T2	1.0	–	–
T3	0.62	0.09 – 4.42	0.61
Biopsy Grade Group			
1 and 2	1.0	–	–
3,4 and 5	**1.66**	**1.35 – 2.04**	**< 0.0001**
Post-operative data			
Pathological stage			
pT2	1.0	–	–
pT3 (a+b)	**2.62**	**2.14 – 3.20**	**< 0.0001**
Pathological Grade Group			
1 and 2	1.0	–	–
3,4 and 5	**2.52**	**2.06 – 3.07**	**< 0.0001**
Positive margins			
No	1.0	–	–
Yes	**2.30**	**1.89 – 2.80**	**< 0.0001**
Lymphadenectomy			
No	1.0	–	–
Yes	**1.48**	**1.19 – 1.83**	**0.0004**

Table 3. Multivariate analyses of BCR risk factors

Variable	**HR**	**95% CI**	***P* value**
PSA (ng/ml)	**1.03**	**1.02 – 1.05**	**< 0.0001**
Pathological Grade Group			
1 and 2	1.0	–	–
3,4 and 5	**2.26**	**1.84 – 2.76**	**< 0.0001**
Pathological stage			
pT2	1.0	–	–
pT3 (a+b)	**1.84**	**1.48 – 2.28**	**< 0.0001**
Positive margins			
No	1.0	–	–
Yes	**1.85**	**1.50 – 2.28**	**< 0.0001**
Lymphadenectomy			
No	1.0	–	–
Yes	1.18	0.94 – 1.48	0.15

Table 4. Univariate analyses for predictive factors of salvage treatment

Variables	**HR**	**95% CI**	***P* value**
Pre-operative data			
Age (years)	1.01	0.99 – 1.03	0.21
PSA (ng/ml)	**1.03**	**1.02 – 1.05**	**0.0001**
Clinical stage			
T1 – T2	1.0	–	–
T3	**12.32**	**1.67 – 90.93**	**0.01**
Biopsy Grade Group			
1 and 2	1.0	–	–
3,4 and 5	**1.63**	**1.29 – 2.06**	**< 0.0001**
Post-operative data			
Pathological stage			
pT2	1.0	–	–
pT3 (a+b)	**1.78**	**1.42 – 2.22**	**< 0.0001**
Pathological Grade Group			
1 and 2	1.0	–	–
3,4 and 5	**1.50**	**1.20 – 1.87**	**0.0004**
Positive margins			
No	1.0	–	–
Yes	**1.72**	**1.38 – 2.15**	**< 0.0001**
Lymphadenectomy			
No	1.0	–	–
Yes	1.22	0.96 – 1.55	0.11

Table 5. Multivariate analyses for predictive factors of salvage treatment

Variable	**HR**	**CI 95%**	***P* value**
PSA (ng/ml)	**1.02**	**1.01 – 1.04**	**0.005**
Pathological Grade Group			
1 and 2	1.0	–	–
3,4 and 5	**1.46**	**1.16 – 1.82**	**0.001**
Pathological stage			
pT2	1.0	–	–
pT3 (a+b)	**1.52**	**1.20 – 1.94**	**0.0006**
Positive margins			
No	1.0	–	–
Yes	**1.45**	**1.14 – 1.84**	**0.002**