Overall, specific, and metastasis-free survival of Afro-Caribbean men with pathological Gleason 6 prostate cancer

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Running title: Survival of men with pathological Gleason 6 prostate cancer

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Abstract

Background

Several studies in the Caucasian population have shown that patients with Gleason 6 prostate cancer, based on surgical specimens, have low or no risk of metastasis. However, there is no data for men of African ancestry. The objective of this study was to estimate the overall, specific, and metastasis-free survival of patients with a Gleason 6 score, based on the surgical specimen.

Patients and methods

This was a monocentric retrospective study that included 723 consecutive patients treated by radical prostatectomy between January 1, 2000 and March 31, 2018, with a Gleason score of 6 based on the surgical specimen. Specific survival was defined as the time elapsed between surgery and death attributed to prostate cancer. Overall survival was defined as the time elapsed between surgery and death from all causes. The causes of death were verified in the medical records. Survival analyses without biochemical recurrence and without salvage treatment were performed according to the Kaplan-Meier method. The Cox model was used for univariate and multivariate analyses.

Results

In total, 691 patients were included because 32 were excluded for missing data. Overall five- and ten-year survival were 94.2% and 87.1%, respectively. Specific survival and metastasis-free survival were 100%, with a median follow-up of 8.5 years. The biochemical recurrence rate was 16.5%, with a median time to biochemical recurrence of 5.1 years. The frequency of salvage treatment was13.0%, with a median time to surgery of 7.3 years. In univariate analysis, PSA, pathological stage, seminal vesicle invasion, positive margins, and lymph node dissection were significantly associated with an increased risk of biochemical

recurrence and salvage treatment, but only PSA and positive margins were significantly associated by multivariate analysis.

Discussion / Conclusion:

No metastasis or disease-specific deaths were observed for men with Gleason score ≤ 6 prostate cancer at radical prostatectomy, in particular, men of African ancestry.

Key words: prostate cancer, radical prostatectomy, Gleason score, survival, metastasis

Introduction

Prostate cancer is the second most common malignancy in men worldwide, accounting for 1,276,106 new cases and causing 358,989 deaths in 2018 [1]. Some have suggested that patients with Gleason 6 prostate cancer have a low potential to become metastatic [2]. Several studies on the Caucasian population have been performed and reported a lower rate of recurrence, lymph node invasion, and metastatic disease in men with Gleason 6 prostate cancer than those with a higher Gleason score [3-7].

Populations of African ancestry display more aggressive disease and a higher worldwide mortality rate from prostate cancer than other ethnic populations [8, 9]. The reasons for such ethnicity-based differences in incidence are largely unknown, but probably involve a complex interplay between hormonal, environmental, and genetic factors [10]. In 2018, Mahal *et al.* reported on their analysis of a database of 403,022 men with localized prostate cancer, showing that black men with Gleason 6 prostate cancer were twice as likely to die than the rest of the sample [11].

Our objective was to estimate overall, specific, and metastasis-free survival in an Afro-Caribbean cohort of patients with pathological Gleason 6 prostate cancer.

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% new cases. Guadeloupe is a French-Caribbean archipelago of 410,000 inhabitants where most of the population (~90%) is of African ancestry. From our cohort of 2,254 men who underwent RP, 723 patients were included between January 1, 2000 and March 31, 2018, of whom 32

were excluded due to missing data. No patients received neoadjuvant hormonal therapy or radiotherapy. Only men classified as having pathological Gleason 6 (3+3) prostate cancer after RP were considered. Before 2005, Gleason grading was applied, whereas afterwards, modified Gleason grading was used, according to the major changes in Gleason grading in 2005 and 2014 [12-14]. All specimens were reviewed by a pathologist of our institution. However, several cases were sent to an expert center for analysis when there was doubt. After surgery, all patients were followed by serial PSA determinations and clinical visits every six months for the first three years and annually thereafter. Biochemical recurrence (BCR) was defined as two consecutive (usually four weeks apart) PSA measurements above 0.2 ng/ml. Metastasis was defined as the presence of prostate cancer in a lymph node or at a distant site with radiological or pathological confirmation.

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 stage, pathological Gleason score, surgical margins, lymphadenectomy status, prostate weight, follow-up PSA, status of dead or living, and cause of death.

Only the medical data from the database of all RPs performed in our department were used. The study was approved by the Ethics Committee of the University Hospital of Guadeloupe.

Statistical analysis

Outcome variables were BCR, defined as the time from RP to BCR; metastasis-free survival (MFS), defined as the time from RP to metastasis (lymph node, distant metastasis, or both); specific survival (SS), defined as the time from RP to death attributed to prostate cancer; and

overall survival (OS), defined as the time from RP to all-cause death. Death and disease-specific death were identified during the review of the medical records.

Survival probabilities were estimated by the Kaplan–Meier method. 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 the 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 March 31, 2018.

The survival rate without salvage treatment was calculated using the Kaplan-Meier method. Time to salvage treatment was defined as the duration between the date of surgery and the date of the beginning of salvage treatment. Univariate and multivariate analyses for salvage treatment were performed as for BCR.

All tests were two-tailed, and P values < 0.05 were considered to be statistically significant.

All analyses were carried out using StatView version 5.0 and MedCalc version 17.5 software.

Results

In total, 691 patients were included in the present study. The median age at the time of surgery was 64.1 years (45.3 – 76.8). The median PSA concentration at diagnosis was 6.8 ng/ml (1.0 – 53.2). Almost all (89.6%) patients had a Gleason score ≤ 6 on biopsy. The baseline characteristics of all patients are summarized in Table 1. A total of 114 patients (16.5%) had BCR with a median time to event of 5.1 years. Ninety men (13%) received salvage treatment with a median time to surgery of 7.3 years. Five- and ten-year OS was

94.2% and 87.1%, respectively. The status of being dead or alive could not be confirmed for 39 patients. However, at the date of the latest news, these patients had low PSA levels, no systemic treatment, and no evidence of local or distant recurrence. The SS and MFS were 100% at five and ten years, with a median duration of follow-up of 8.5 years.

In the survival analysis, there was a significant difference between pT2 and pT3 pathological stage for five- (HR = 2.11; 95% CI [1.01 – 4.41], p = 0.008) and ten-year BCR-free survival (HR = 2.29, 95% CI [1.22 – 4.29], p = 0.0004). There was also a significant difference between positive margins or not for five- (HR = 3.26 ; 95% CI [1.87 – 5.69], p < 0.0001) and ten-year BCR-free survival (HR = 2.74, 95% CI [1.68 – 4.46], p = 0.0001). All data for significant BCR-free survival are summarized in Figure 1. We obtained similar results for time to salvage treatment-free survival (summarized in Figure 2).

In univariate analysis, predictive factors associated with BCR were PSA, pathological stage (pT3), seminal vesicle invasion (pT3b), positive surgical margins, and lymphadenectomy (Table 2). High PSA (p < 0.005) and positive margins (p = 0.01) were factors for BCR in multivariate analysis (Table 3). The results were similar for uni- and multivariate analysis for salvage treatment (summarized in Tables 4 and 5).

Discussion

This is the first study to investigate MFS, SS, and OS for men with Gleason 6 prostate cancer based on RP specimens in an Afro-Caribbean population. The strengths of our study include the small amount of missing data, the number of patients included, and the median follow-up of 8.5 years. This population is known to have one of the highest incidences of prostate cancer in the world and more aggressive disease, with a higher Gleason score than Caucasian men [15]. We show a negligible potential for prostate cancer metastasis and death for men with

Gleason ≤ 6 prostate cancer treated by RP. Previous studies have reported similar results in the Caucasian population. No metastasis or disease-specific deaths were observed for men with pathological Gleason ≤ 6 with similar baseline characteristics: for example, median age of 64 years, PSA at diagnosis of 6.2 ng/ml, extracapsular extension in 17% of cases, invasion of seminal vesicles in 0.4% of cases, and 20% with a positive surgical margin [7, 16].

Unlike many tumors, prostate cancer is a heterogeneous disease and susceptible to sampling error. The average rate of upgrading between biopsy Gleason score and surgical specimen Gleason score is approximately 30%. This finding does not allow extrapolation of survival data based on the pathological Gleason score of 6 to the Gleason score of 6 based on biopsies. Epstein *et al.* showed that 20% of the surgical specimens from a cohort of 7,643 prostatectomies had a tertiary grade pattern. Of the 5,071 cases of Gleason 5-6 at biopsy, only 63.7% were Gleason 5-6 after RP and 11.2% Gleason 6 with tertiary grade, the remainder (25.1%) being classified Gleason ≥ 7. Finally, 12.4% and 3.6% of cases had a Gleason score at biopsy of 7 (3+4) and 7 (4+3), respectively, with a Gleason 6 plus tertiary at RP [17]. Furthermore, in our present study, 7.2% of Gleason 6 prostate cancer had extra prostatic expansion (pT3a) and 2.7% seminal vesicle involvement, indicating that these tumors can show locally aggressive behavior.

Limitations of our study were its retrospective nature and the absence of the review of cases after modification of the grading score system. However, the modifications of the Gleason score only led to the reclassification of grade 3 to grade 4. The grading system was reviewed by the International Society of Urological Pathology (ISUP) at the 2005 consensus conference. In the modified criteria, poorly defined glands with poorly formed glandular lumina, large cribriform glands with smooth edges, and the glomeruloid glands classically described as grade 3 adenocarcinoma were redefined as grade 4 [18], whereas the last ISUP consensus conference in 2014 redefined the Gleason score into five prognostic groups [19]. In

our study, two patients with metastasis were classified as Gleason 7 after review and were excluded. In 2012, Dong *et al.* reviewed the specimens of 806 patients treated by RP with Gleason 6 and Gleason 7 scores (3+4), according to the modified grading system. The review of Gleason 6 specimens led to upgrading to Gleason 7 for 34% according to modified ISUP criteria. In contrast, no case of Gleason 7 (3+4) was reclassified as Gleason 6 [20].

One of the main challenges over the next few years will be to unambiguously detect men with Gleason 6 prostate cancer, without upgrading based on surgical specimens. This will probably occur due to improved imaging techniques, better knowledge of molecular biology, and the development of artificial intelligence.

Conclusion

In conclusion, no metastasis or disease-specific deaths were observed for men with Gleason score ≤ 6 prostate cancer at RP, in particular, that of men of African ancestry.

Words account: 1657

Acknowledgement

There is no particular acknowledgement for this work.

Conflict of interest

The authors declare that they have no conflict of interest.

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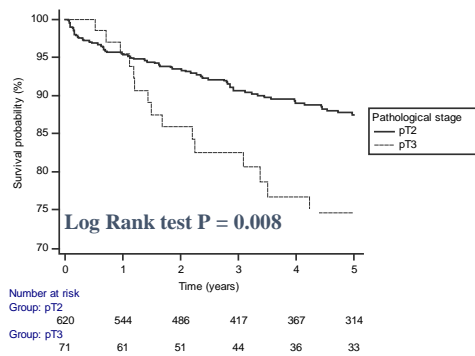
Figure legends

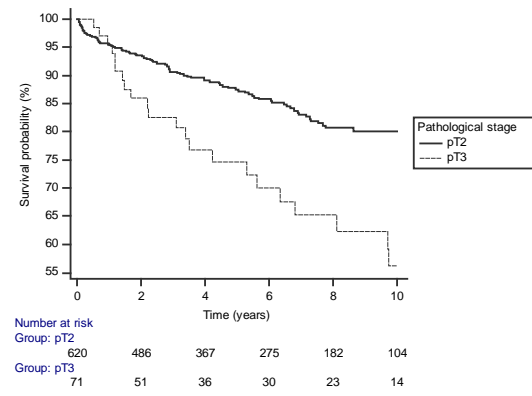**Figure 1. Five- and ten-year BCR-free survival**

    a- Pathological stage (5 years)

    b- Pathological stage (10 years)

    c- Seminal vesicle invasion (5 years)

    d- Seminal vesicle invasion (10 years)

    e- Surgical margins (5 years)

    f- Surgical margins (10 years)
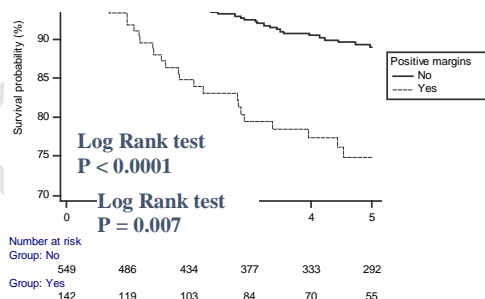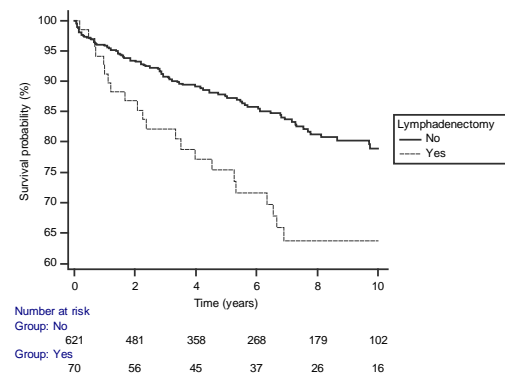
    g- Lymphadenectomy (5 years)

    h- Lymphadenectomy (10 years)

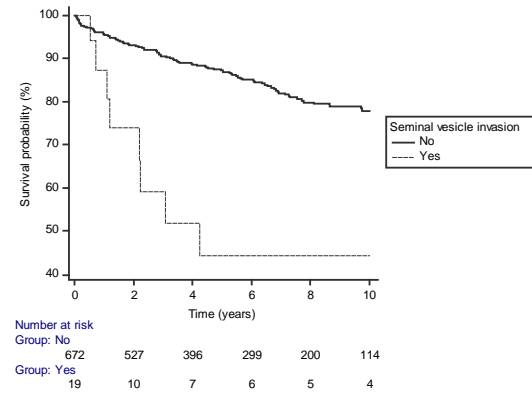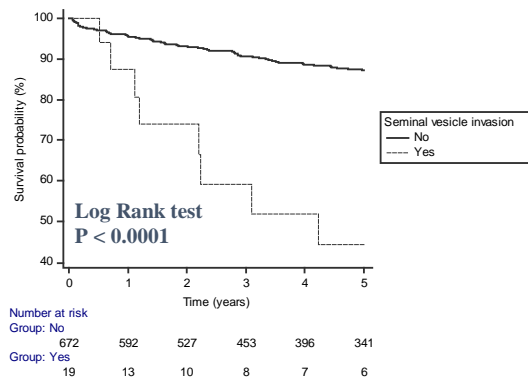**Figure 2. Survival analysis for time to salvage treatment**

    a- Pathological stage

    b- Seminal vesicle invasion

    c- Surgical margins

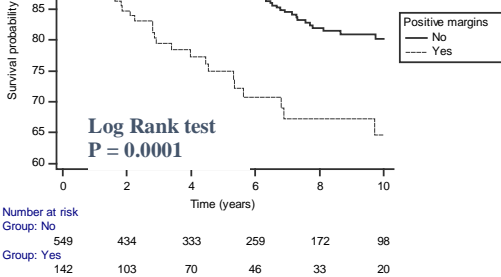   d- Lymphadenectomy

a-

Log Rank test P = 0.008

Pathological stage (5 years)

c- Seminal vesicle invasion (5 years)

e- Surgical margins (5 years)

d- Seminal vesicle invasion (10 years)

Log Rank test P = 0.0001

f- Surgical margins (10 years)

Log Rank test P < 0.0001

Log Rank test P = 0.007

g-

h- Lymphadenectomy (10 years)

Lymphadenectomy (5 years)

Figure 1. Five- and ten-year BCR-free survival

b- Pathological stage (10 years)

Log Rank test P = 0.002

Log Rank test P = 0.0001
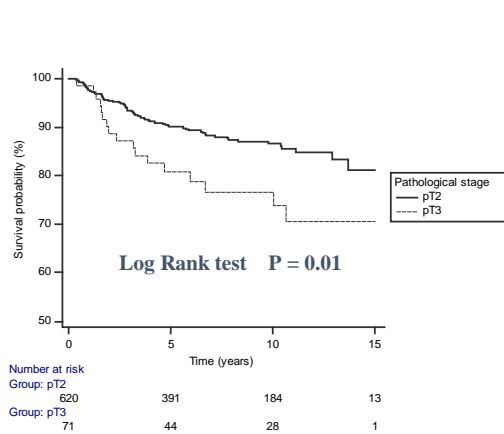
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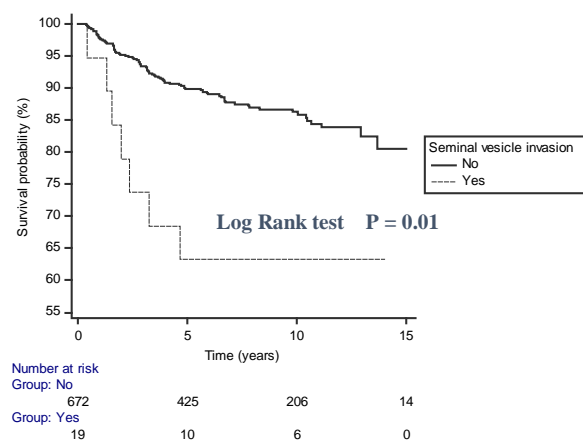
b- Seminal vesicle invasion
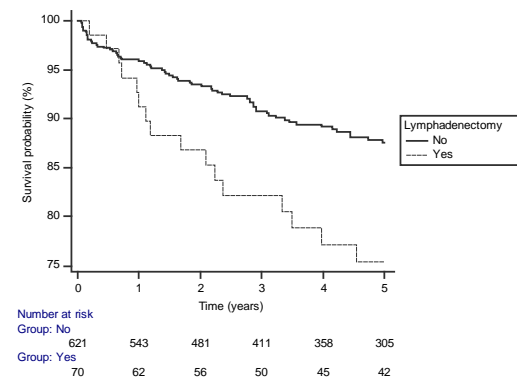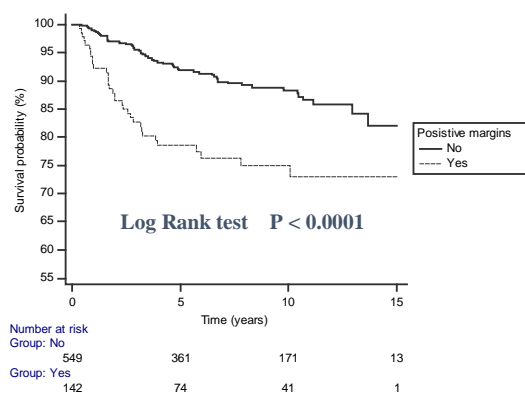

c- Surgical margins
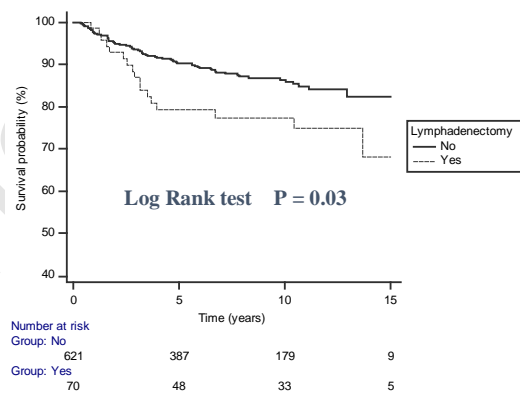
d- Lymphadenectomy

Figure 2. Survival analysis for time to salvage treatment

Tables and their legends

Table 1. Baseline characteristics of all patients

Table 2. Univariate analyses of BCR risk factors

Table 3. Multivariate analyses of BCR risk factors

Table 4. Univariate analyses for predictive factors of salvage treatment

Table 5. Multivariate analyses for predictive factors of salvage treatment

Table 1. Baseline characteristics of all patients

Variables	TOTAL
Number of patients (%)	691 (100%)
	Median (range)
Age at surgery (years)	64.1 (45.3 – 76.8)
PSA at diagnosis (ng/mL)	6.8 (1.0 – 53.2)
Follow up (years)	8.5 (0.2 – 19.1)
Time to BCR (years)	5.1 (0.3 – 15.0)
Duration between surgery and salvage treatment (years)	7.3 (0.3 – 18.0)
	Number (%)
Clinical stage	
T1	447 (64.7)
T2	226 (32.7)
Missing data	18 (2.6)
Biopsy ISUP score:	
1 (≤ 6)	619 (89.6)
2 (3+4)	45 (6.5)
3 (4+3)	14 (2.0)
4 (8)	5 (0.7)
Missing data	8 (1.2)
Prostate specimen:	
- Pathological stage:	
pT2	620 (89.7)
pT3 – pT4	71 (10.3)
- Extra capsular extension (pT3a):	
No	641 (92.8)
Yes	50 (7.2)
- Seminal vesicles invasion (pT3b):	
No	672 (97.3)
Yes	19 (2.7)
- Positive surgical margins:	
No	549 (79.5)
Yes	142 (20.5)
Lymphadenectomy:	
No	621 (89.9)
Yes	70 (10.1)
Biochemical recurrence	
No	577 (83.5)
Yes	114 (16.5)
Salvage treatment	
No	601 (87.0)
Yes	90 (13.0)
Death	
No	568 (82.2)
Yes	84 (12.2)
Missing data	39 (5.6)
Causes of death	
Cardiovascular diseases	15 (17.8)
Other cancers	26 (31.0)
Other causes	43 (51.2)

Table 2. Univariate analyses of BCR risk factors

Variables	HR	95% CI	*P* value
Age (years)	1.00	0.98 – 1.03	0.76
PSA (ng/ml)	**1.06**	**1.03 – 1.09**	**< 0.0001**
Pathological stage			
pT2	1.0	–	–
pT3 (a+b)	**2.24**	**1.41 – 3.54**	**0.0006**
Extracapsular Invasion			
No	1.0	-	-
Yes	1.63	0.93 – 2.85	0.09
Seminal vesicles invasion			
No	1.0	-	-
Yes	**3.56**	**1.73 – 7.31**	**0.0006**
Positive margins			
No	1.0	–	–
Yes	**2.18**	**1.47 – 3.23**	**0.0001**
Lymphadenectomy			
No	1.0	–	–
Yes	**2.00**	**1.27 – 3.16**	**0.003**

Table 3. Multivariate analyses of BCR risk factors

Variables	HR	95% CI	*P* value
PSA (ng/ml)	**1.04**	**1.01 – 1.08**	**< 0.005**
Pathological stage			
pT2	1.0	–	–
pT3 (a+b)	1.60	0.98 – 2.61	0.059
Positive margins			
No	1.0	–	–
Yes	**1.73**	**1.14 – 2.64**	**0.01**
Lymphadenectomy			
No	1.0	–	–
Yes	1.40	0.86 – 2.29	0.18

Table 4. Univariate analyses for predictive factors of salvage treatment

Variables	HR	95% CI	*P* value
Age (years)	1.00	0.97 – 1.04	0.83
PSA (ng/ml)	**1.06**	**1.03 – 1.09**	**0.0004**
Pathological stage			
pT2	1.0	–	–
pT3 (a+b)	**1.94**	**1.14 – 3.30**	**0.014**
Extracapsular Invasion			
No	1.0	-	-
Yes	1.26	0.63 – 2.51	0.52
Seminal vesicles invasion			
No	1.0	-	-
Yes	**3.38**	**1.56 – 7.31**	**0.002**
Positive margins			
No	1.0	–	–
Yes	**2.54**	**1.65 – 3.90**	**< 0.0001**
Lymphadenectomy			
No	1.0	–	–
Yes	**1.77**	**1.04 – 3.03**	**0.035**

Table 5. Multivariate analyses for predictive factors of salvage treatment

Variables	HR	95% CI	*P* value
PSA (ng/ml)	**1.05**	**1.01 – 1.09**	**0.013**
Pathological stage			
pT2	1.0	–	–
pT3 (a+b)	1.27	0.73 – 2.24	0.40
Positive margins			
No	1.0	–	–
Yes	**2.19**	**1.38 – 3.48**	**0.0008**
Lymphadenectomy			
No	1.0	–	–
Yes	1.24	0.70 – 2.18	0.46