Late Biochemical Recurrence Post-Prostatectomy is Associated with a Slower Rate of Progression

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Abstract

Objective:

To characterise the pattern of late disease recurrence in the largest contemporary cohort of localised prostate cancer patients treated with radical prostatectomies in the active surveillance era.

Patients and Methods:

Consecutive patients who underwent radical prostatectomy for localised prostate cancer between 2003 and 2017 were identified from a prospectively recorded, dedicated prostate cancer database. Patients who received neo-adjuvant androgen deprivation therapy were excluded. These patients were categorised into no recurrence; <12 months (early); 12-60 months (intermediate); and >60 months (late). Clinicopathological characteristics were analysed using Student's t-test, Mann-Whitney U test, or Chi-square tests where appropriate. Multivariable binomial logistic regression models were performed to assess predictors of recurrence at various time-points.

Results:

Total of 2312 patients were included in the final analysis with up to 12 years of follow up data. The average patient had clinically localised prostate cancer, an elevated PSA, and ISUP grade group 2 on biopsy. 88.7% of patients had ISUP grade group 2 or higher at prostatectomy. A subgroup of 446 patients had undetectable PSA levels at 5 years after prostatectomy; 11.7% of them progressed to experience biochemical recurrence. In this subgroup, late recurrers had significantly higher-grade tumours on ISUP and Gleason sum ($p = <0.001$ and $p = 0.001$, respectively), higher rates of extraprostatic extension ($p = 0.022$), and larger tumour volumes ($p = 0.032$). Logistic regression demonstrated that prostatectomy ISUP grade group was a significant predictor (OR 2.14, 95% CI 1.43-3.20, $p = <0.001$).

Conclusion:

This study characterises the pattern of late recurrence in the largest contemporary active surveillance era cohort. We have identified that prostatectomy ISUP grade group is a strong predictive indicator for late recurrence. We also propose that timing of recurrence resides on a continuum of risk and that the potential concept of dormant micrometastatic involvement requires further research and evaluation.

Keywords:

Late biochemical recurrence, active surveillance era, prostate cancer, prostatectomy

Introduction

Radical prostatectomy is the preferred initial treatment for localised prostate cancer in 59% and 45% of men with localised prostate cancer in Europe and the United States, respectively [1, 2]. Although the majority experience long term disease control, depending on the pre-treatment clinical characteristics of the cohort under study, up to a third of men will develop disease recurrence [3-5]. The most common manifestation of disease recurrence is a detectable serum PSA in the postoperative period, with current European Association of Urology guidelines defining biochemical recurrence (BCR) as a PSA measurement of ≥ 0.2 ng/ml following prostatectomy with a second confirmatory reading of the same level or higher [6].

Conceptually, post prostatectomy BCR may represent failure of surgery to eradicate all local (and possibly regional) disease (treatment failure), or subclinical metastatic dissemination that is not detectable by current imaging (staging failure), or a combination of the two.

Although commonly considered as discrete clinical entities, recent genomic studies suggest the inter-relationship between local recurrence and metastases is more complex [7]. Either way, treatment decisions regarding the choice of treatment (salvage radiotherapy vs. androgen deprivation therapy) are commonly informed by both the time to recurrence as well as rapidity of the PSA rise [8]. For instance, in the absence of definitive imaging findings, an early recurrence with a rapid PSA doubling time may be taken as evidence as a systemic rather than a local recurrence, and may lead to the selection of ADT rather than salvage RT as the preferred treatment option.

Given the long natural history of prostate, its high prevalence in the community as well as increasing competing mortality risks with aging, the optimal duration of post prostatectomy

PSA surveillance in the specialist setting is unclear. In many health care settings, a pragmatic approach may be taken, with patients who are disease free for 5 years being discharged back to their local doctor for ongoing care. However, older long term data suggest that up to 23.4% of patients will recur after this time, with the development of clinical recurrence and metastases reported up to 18% within 15 years after presumed curative treatment [5].

Given the profound changes that have occurred in prostatectomy cohorts due to the rise of active surveillance for low risk disease, we aimed to characterise the pattern of late disease recurrence in a contemporary cohort.

Patients and methods

Patient Selection

Consecutive patients undergoing prostatectomy for localised prostate cancer with participating surgeons from December 2003 to March 2017 at the Epworth Hospital Richmond were identified from a prospectively recorded, dedicated prostate cancer database, totalling 2351 patients. 39 patients who received neo-adjuvant androgen deprivation therapy were excluded from the analysis, leaving a final cohort of 2312 patients. Biochemical recurrence was defined as a postoperative serum PSA of ≥ 0.2 ng/mL, or a PSA level below this that was considered by the treating physician to represent disease recurrence, and led to the initiation of salvage therapies. The characteristics of the patients who had initiation of salvage therapies with a serum PSA of < 0.2 ng/mL are described in Table S1. Patients were categorised into the following groups defined by the time taken for recurrence (if applicable) to develop: no recurrence; < 12 months (early); 12-60 months (intermediate); and > 60 months (late). The decision to describe late recurrence as greater than 5 years from surgery was pragmatic, as this time point is frequently the time that treating urologists in our institution begin considering transferring follow-up management to community general practitioners. The collection and use of this data was institutionally reviewed and approved.

Statistical Analysis

Continuous data are presented as median with interquartile ranges, with differences between groups analyzed using either Student's t-test or Mann-Whitney U test (or the Kruskal-Wallis for multiple independent groups) where appropriate. Categorical data is presented as percentages, with differences between groups determined by Chi-square tests. To assess predictors of recurrence at various time-points, binomial logistic regression models were

fitted, and odds ratios calculated. Kaplan-Meier was used in estimating conditional survival. All analyses were performed using SPSS (IBM). All tests were two-sided, with significance assumed at $p < 0.05$.

Calculation of tumour volume

Digital planimetry was utilised in the calculation of total tumour volume as previously described by Hong et al. [9] In summary, every specimen was routinely fixed in formalin and sliced at 4-5mm intervals from apex to base. 5 μ m section was subsequently taken, stained with haematoxylin and eosin, and the tumour borders marked by pen. These were digitally scanned and tumour areas determined. Tumour volumes were calculated by summation of all tumour area sections multiplied by section thickness. No shrinkage factor for applied for this study. In the case of multifocal tumours, the volumes of each individual tumour were summated to provide a total tumour volume for each patient.

Calculation of PSA doubling time

Calculations of PSA doubling time, were performed as per recommendations of Daskivich et al. [10] using the log slope method. The starting point commenced when PSA became detectable and the end point was defined as the initiation of salvage therapies, being medical, surgical or radiation. A minimum interval of 3 months between measurements was selected. For patients who had PSA-persistence following their radical prostatectomy and salvage therapy was commenced immediately, their PSA doubling time was arbitrarily defined as < 3 months. Patients who had recorded PSA measurements greater than ≥ 0.2 ng/mL post-operatively and subsequently had a decline of over 50% in value were assumed to have undergone salvage therapy despite the absence of a record of such therapy; this was only for the purpose of calculating PSA doubling time ($n = 41$). 112 patients had no or insufficient follow up PSA measurement data to accurately calculate a PSA doubling time.

Results

The total number of participants included in the final analysis was 2312, the clinical and pathological characteristics of which are summarised in Table 1. The average patient in the cohort was 62 years old at time of surgery, had clinically localised disease associated with an elevated PSA, and had an ISUP grade group 2 tumour on biopsy. At prostatectomy, the majority similarly had ISUP grade group 2 disease. Seminal vesicle invasion and extra

prostatic extension were observed in 7.5% and 35.4% of patients respectively. Complication rates for this cohort has been previously described by Murphy et al. [11] Up to 12 years of follow up data was available with a median of 30 months (IQR 12-59) for patients who did not experience biochemical recurrence. Over this time 21.2% of patients experienced a biochemical recurrence, with the majority (n = 219) occurring within the first 12 months (Figure 1), however there was a long tail extending beyond 5 years.

Patients were then categorised by time taken for BCR to develop, and their clinical and pathological characteristics then compared (Table 2). Comparing patients who experienced a late recurrence with those who did not recur, late recurrers had significantly higher-grade tumours as measured by both ISUP grade group and Gleason sum ($p = 0.001$ and $p = 0.015$, respectively). Despite significant differences in the variables utilised for pre-operative risk assessment, including clinical T-stage ($p = 0.018$), biopsy ISUP grade group ($p = 0.001$), and biopsy Gleason sum ($p = 0.014$), there were no other significant differences in relevant pathological variables at prostatectomy.

In order to provide a better comparison between the no recurrence and late recurrence cohorts, and to avoid an immortal time bias, we limited the analysis of clinical and pathological characteristics to only patients with greater than 60 months of follow up which is the minimum amount of follow up required for a patient to be considered for late recurrence (Table 3). In this analysis, the significant variables from the previous analysis retained their significance; however, a greater number of pathological features were in addition, significantly different. The late recurrers had larger tumour volumes (2.7cc vs. 1.9cc, $p = 0.032$) as well as higher rates of extraprostatic extension (34.6% vs. 20.6%, $p = 0.022$). However, when logistic regression analysis was performed to identify the most relevant independent factors associated with late recurrence, prostatectomy ISUP grade group was the only significant predictor with OR 2.14 (95% CI 1.43-3.20, $p = <0.001$), indicating that it is the most important tumour characteristic determining late recurrence risk (Table 4).

When comparing the clinical characteristics between the late and early recurrence groups, the late recurrers had clinically lower risk pre-operative attributes such as lower PSA (6.5 vs. 9.0 ng/mL, $p = <0.001$), fewer clinically palpable prostates (clinical T-stage, $p = 0.042$), and lower ISUP grade groups on prostate biopsies ($p = 0.006$). A similar pattern was observed with pathological characteristics at prostatectomy; late recurrers had less aggressive disease

as determined by both ISUP grade groups ($p = <0.001$) and pathological T-stage ($p = <0.001$). They have also had lower rates of seminal vesicle invasion (4.1% vs. 31.4%, $p = <0.001$), extraprostatic extension (34.6% vs. 69.5%, $p = <0.001$), pathological margin positivity (19.2% vs. 52.1%, $p = <0.001$), and smaller tumour volumes (2.7cc vs. 5.9cc, $p = <0.001$). On logistic regression, pathological T-stage and positive pathological margins were demonstrated to be strongly associated with early recurrence when compared to late recurrence with OR 2.34 (95% CI 1.08-5.08, $p = 0.03$) and OR 2.97 (95% CI 1.36-6.49, $p = <0.01$), respectively (Table S2). When comparing early recurrence with no recurrence on logistic regression, the significant predictors were pathological T-stage (OR 2.19, 95% CI 1.51-3.16, $p = <0.001$), prostatectomy ISUP grade group (OR 2.93, 95% CI 2.37-3.62, $p = <0.001$), and positive pathological margin (OR 2.98, 95% CI 2.11-4.22, $p = <0.001$); as shown in Table S3.

To determine if the rate of progression was associated with the timing of recurrence, we calculated PSA doubling time for each recurrent patient, which has previously been shown to be a significant predictor of metastasis-free and cancer-specific survival [5, 12]. Patients who experienced recurrence >5 years post prostatectomy were observed to have a significantly longer PSA doubling time compared to both early and medium term recurrers, with the majority of late recurrers demonstrating doubling times greater than 12 months, whilst the majority of early recurrers had doubling times less than 3 months ($p = <0.001$). In patients who experienced late recurrence, 47 of 52 patients had an initial detectable PSA of <0.2 ng/ml. The median serum PSA was 0.035 ng/ml and the median time post-operatively to patients having a detectable PSA was 21.5 months. Median duration between first detectable PSA and time of recurrence was 59.3 months. Subsequently, we calculated the PSA doubling time for measurements pre-BCR (<0.2 ng/ml) and post-BCR (≥ 0.2 ng/ml). The pre-BCR group had longer PSA doubling times at 21.1 months compared to post-BCR at 18.0 months. However, in a small number of cases, rapid progression was still observed despite the long interval between surgery and recurrence.

Another point of interest was to determine the likelihood of an individual remaining BCR-free given that they have already survived a set number of years without progression. In order to perform this, conditional survival (CS) was estimated as previously described [13-15]. Overall 5-year BCR-free survival was 81.0%. On the other hand, probability for 5-year BCR-

free survival for patients who have already survived BCR-free after surgery for 1, 2, 3, and 4 years was 89.4% (+10.3%), 92.8% (+14.6%), 96.5% (+19.1%), and 98.7% (21.9%), respectively. This is also shown for 10-year BCR-free survival; 78.9%, 87.1% (+10.4%), 90.3% (+14.4%), 94.0% (+19.1%), 96.2% (+21.9%), and 97.4% (+23.4%) for already surviving BCR-free for 0, 1, 2, 3, 4, and 5 years after surgery, respectively (Figure 2).

Discussion

A significant proportion of patients who undergo radical prostatectomy for primary treatment of prostate cancer will unfortunately experience biochemical recurrence [16]. The majority of studies reporting such recurrence focus on overall or early incidence, with some studies indicating that it can occur up to a third of all cases. [3-5, 17, 18]. Only a handful of studies have focused on late recurrence, which is the most relevant in assisting clinicians in determining the appropriate length of follow-up for patients who have not already experienced a post-prostatectomy BCR event. For instance a study of 10,609 men from John Hopkins Hospital who underwent radical prostatectomy for localised prostate cancer found that 3.6% of patients went on to develop BCR after having an undetectable PSA during their initial 5 years of follow-up [19]. Given that the study population extends back to 1978 and only 24.0% of their patients had a biopsy Gleason sum of 7 or greater, this study may not be reflective of contemporary risk profiles, due to a significant proportion of men with low risk disease now opting for active surveillance [20]. In a more contemporary cohort study of 478 patients (76% of whom had Gleason score 7 or greater), Negishi et al. observed that biochemical recurrence occurred in 28.2% of the patients studied, with 4.6% of the total study group having BCR after 5 years [21]. With the lack of studies in the active surveillance era, our contemporary cohort of 2312 men represents the largest to date. This is highlighted by 88.7% of patients having underwent radical prostatectomy for Gleason score greater or equal to 7, 491 (21.2%) patients experienced overall BCR, and 52 (2.2%) patients developing a recurrence after having an undetectable PSA for at least 5 years postoperatively.

To date, there are only a handful of studies which specifically analyze predictors for late BCR after prostatectomy. In the study by Aho et al., the predictive factors on univariate analysis for late BCR when compared to no recurrence were higher Gleason sum, extraprostatic extension, seminal vesicle invasion, and pathological margin status [22]. These indicators stayed significant on multivariate analysis except for seminal vesicle invasion and pathological margin status. This cohort had similar pathological characteristics to our study

population regarding T-stage and margin status. However, the cohort from Aho et al. had higher proportions of low-risk disease; 58% had Gleason score of 6 compared to only 24.8% in our cohort. Caire et al. studied 1207 men who had BCR post-prostatectomy and were further stratified into groups of early BCR (<5 years) and late BCR (>5 years). They found that the predictors for late BCR on both univariate and multivariate analyses were lower pre-operative PSA and lower prostatectomy Gleason sum [17]. We also similarly concluded that lower pathological Gleason sums were predictive of late BCR. On the other hand, pre-operative PSA was only significant in our study on univariate analysis between BCR occurring before 12 months and BCR occurring after 5 years ($p = <0.001$). In another large study by Loeb et al. at Johns Hopkins Hospital, it was demonstrated that late BCR patients were typically more likely to have lower pathological T-stage ($p = <0.0001$) and fewer positive surgical margins ($p = 0.0003$) [19]. The findings from this current study are in line with these previously reported results by Aho et al, Caire et al, and Loeb et al.; additionally, we found that clinical T-stage ($p = 0.042$), biopsy Gleason sum ($p = 0.006$), biopsy ISUP grade group ($p = 0.004$), and all other pathological variables ($p = <0.001$) were significantly different within our cohort when comparing early versus late BCR (Table 2). Ward et al. reported significantly longer median PSA doubling times in patients with BCR occurring after 5 years following surgery compared to those who had BCR within 5 years of surgery, 5.3 versus 1.5 years, respectively [23]. In a comparison of PSA doubling times of <3 months and ≥ 15 months, Freedland et al. highlighted a markedly higher chance of prostate cancer-specific death in the PSA doubling times of <3 months cohort (HR 27.48; 95% CI 10.66-70.85; $p = <0.001$) [24] indicating that longer PSA doubling times are associated with a less aggressive phenotype. In our analysis we grouped PSA doubling times into 3-month brackets and similarly demonstrated that patients with late BCR had longer PSA doubling times when compared to early BCR ($p = <0.001$) and intermediate BCR ($p = <0.001$). There was a progressive shift between the brackets from shorter (<3 months) to longer (>12 months) PSA double times as it moved from early, to intermediate, and to late recurrence cohorts (Table 2), suggesting a continuum of disease progression in which time to recurrence is potentially an important determinant.

Certainly this 'continuum of risk' is supported by the association between tumour grade of disease and timing of recurrence. It is reported that late BCR patients have lower tumour grades compared patients with early BCR [17, 22, 23, 25]. This is also seen in our cohort

when comparing the late versus no recurrence groups ($p = 0.015$), as well as the late versus early groups ($p = 0.001$). Combined with other factors that are also significantly associated with late PSA recurrence, this points towards a more intermediary picture of aggressiveness that lies between the early and no recurrence cohorts. These other factors include extracapsular extension, seminal vesicle invasion, positive margin status as described by Aho et al. [22]; PSA at diagnosis and pathological T-stage demonstrated by Lisenfeld et al. [25]; as well as higher tumour volume and higher-risk stratification on clinical diagnosis in this current study. This association with incremental increases in adverse pathological features suggests that there may already be sites of micrometastasis present at time of surgery, which are perhaps being kept in a dormant state [26].

If the concept of dormant micrometastatic sites holds true for late recurrence, it is reasonable to speculate why these sites become re-activated. Cancer immune surveillance is a model where the human immune system protects itself from cancer progression in order to maintain cellular homeostasis [27]. Given that prostate cancer mainly affects men in their later stages of life, their cancer immunosurveillance may be starting to fail; therefore, allowing the once dormant cancerous cells to flourish and become detectable as a late recurrence. This is an interesting area for further research especially with the development of newer techniques for identifying sites of micrometastatic disease.

As the risk of prostate cancer recurrence sits on a continuum, it adds to the complexity of determining the appropriate follow-up plan for these patients. Currently the European Association of Urology guidelines [6] recommends annual PSA measurements past 3 years after radical prostatectomy while the American Urological Association does not outline a specific post-prostatectomy plan for PSA testing [28]. Within our cohort of 2312 patients, 2.2% ($n = 52$) experienced BCR beyond 5 years post-radical prostatectomy. This mirrors other internationally reported figures [5, 17, 19, 21]. Additionally, prostatectomy ISUP grade group was an independent predictor on logistic regression analysis comparing no recurrence to late BCR in a subset of patients with greater than 60 months of follow-up (OR 2.14; 95% CI 1.43-3.20; $p = <0.001$). Considering that the risk of recurrence is a continuum, we believe that patients with higher ISUP grade groups and/or the presence of aggressive pathological features warrant longer follow-up past 5 years. This view is also supported by Aho et al. as they found patients with factors such as extraprostatic extension, seminal vesicle invasion, and high Gleason scores still have a considerable risk of developing BCR despite having 5

years of undetectable PSA measurements [22]. To lessen the burden on patients and treating urologists, patients who have undetectable PSA measurements for 5 years and do not exhibit any aggressive features may be further managed by their family physician in their community. This is also supported with the CS results where by individuals that already survived 5 years BCR-free have a 23.4% advantage over those who have not when comparing 10-year BCR-free survival (Figure 2). Additionally, a slowly rising PSA could potentially arise from a benign cause; however, it is always important to ensure a urological contingency plan is in place if PSA becomes detectable.

A limitation of this study is that the patient population was selected from a single institution in Australia; therefore, the findings may not be consistent with other worldwide patient populations. The surgical technique utilised for all patients was robotic assisted radical prostatectomy (RARP). The effect of the learning curve on late recurrence is demonstrated in Table S4. Surgeons at our institution do not routinely perform lymph node dissections. This may have an impact when comparing the findings with other studies of late recurrence which employ other surgical techniques. The group of interest, patients who develop late recurrence, is also limited by its relative small sample size; however, its proportion is similar to other international reports.

In conclusion, we have characterised the pattern of late recurrence in patients undergoing radical prostatectomy for localised prostate cancer and identified that prostatectomy ISUP grade group is a strong predictive indicator for late recurrence. We also propose that timing of recurrence resides on a continuum of risk and that the potential concept of dormant micrometastatic involvement requires further research and evaluation.

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Legends for Figures

Figure 1. Histogram demonstrating the incidence of patients experiencing biochemical recurrence post-prostatectomy. A total number of 2312 patients undergoing prostatectomy were included in the study, of whom 491 patients experienced BCR.

Figure 2. Conditional survival curves indicating BCR-free survival over time depending on the years elapsed from time of surgery. The table demonstrates the probability of being BCR-free at a given timepoint based on how many years have elapsed being BCR-free after prostatectomy.

Age at Surgery	Median	62
	IQR	57-66
PSA	Median	6.4
	IQR	4.8-9.0
Clinical Stage	T1	1459 (63.9%)
	T2	759 (33.2%)
	T3	67 (2.9%)
Biopsy Gleason Sum	≤6	672 (29.2%)
	7	1338 (58.0%)
	≥8	295 (12.8%)
Biopsy ISUP Grade Group	1	662 (28.8%)
	2	969 (42.2%)
	3	369 (16.1%)
	4-5	295 (12.9%)
pT	2	1492 (64.8%)
	3	812 (35.2%)
Prostatectomy Gleason Sum	≤6	261 (11.3%)
	7	1787 (77.7%)
	≥8	252 (11.0%)
Prostatectomy ISUP Grade Group	1	261 (11.3%)
	2	1211 (52.7%)
	3	576 (25.0%)
	4-5	252 (11.0%)
SVI	No	2094 (92.5%)
	Yes	171 (7.5%)
EPE	No	1485 (64.6%)
	Yes	813 (35.4%)
Pathological margin	Negative	1776 (77.2%)
	Positive	525 (22.8%)
Tumour volume	Median	2.4
	IQR	1.2-4.7

Recurrence	No	1821 (78.8%)
	Yes	491 (21.2%)
Follow up	Median	27
	IQR	9-53
PSA Doubling Time	Median	13.5
	IQR	6.1-22.0

Table 1. Clinical and pathological characteristics of the study cohort. pT = pathological T-stage; EPE = extraprostatic extension; SVI = seminal vesicle invasion.

Recurrence Group		No recurrence	<12 months	12-60 months	>60 months	p-value (>60mths vs no recurrence)	p-value (>60mths vs <12mths)	p-value (>60mths vs 12-60mths)
n = 2312		1821 (78.8%)	219 (9.5%)	220 (9.5%)	52 (2.2%)			
Age	Median	62	63	63	62	0.732	0.109	0.205
	IQR	57-66	58-68	58-67	57-65			
PSA	Median	6.0	9.0	7.4	6.5	0.327	<0.001	0.615
	IQR	4.7-8.3	6.4-16.8	5.6-10.8	5.4-9.0			
cT	1	1237 (68.7%)	88 (41.3%)	106 (48.4%)	28 (53.8%)	0.018	0.042	0.404
	2	543 (30.1%)	96 (45.1%)	98 (44.7%)	22 (42.3%)			
	3	21 (1.2%)	29 (13.6%)	15 (6.8%)	2 (3.8%)			
Biopsy Gleason Sum	≤6	585 (32.2%)	34 (15.6%)	43 (19.5%)	10 (19.2%)	0.014	0.006	0.210
	7	1091 (60.1%)	98 (45.0%)	115 (52.3%)	34 (65.4%)			
	≥8	139 (7.7%)	86 (39.4%)	62 (28.2%)	8 (15.4%)			
Biopsy ISUP Grade Group	1	578 (32.0%)	31 (14.4%)	43 (19.5%)	10 (19.2%)	0.001	0.004	0.188
	2	837 (46.3%)	53 (24.7%)	60 (27.3%)	19 (36.5%)			
	3	254 (14.0%)	45 (20.9%)	55 (25.0%)	15 (28.8%)			
	4-5	139 (7.7%)	86 (40.0%)	62 (28.2%)	8 (15.4%)			
pT	2	1299 (71.5%)	66 (30.7%)	93 (42.3%)	34 (65.4%)	0.337	<0.001	0.003
	3	518 (28.5%)	149 (69.3%)	127 (57.7%)	18 (34.6%)			
Prostatectomy Gleason Sum	≤6	239 (13.2%)	11 (5.2%)	8 (3.7%)	3 (5.8%)	0.015	0.001	0.101
	7	1470 (80.9%)	115 (54.0%)	160 (73.1%)	42 (80.8%)			
	≥8	107 (5.9%)	87 (40.8%)	51 (23.3%)	7 (13.5%)			
Prostatectomy ISUP Grade Group	1	239 (13.2%)	11 (5.2%)	8 (3.7%)	3 (5.8%)	0.001	<0.001	0.046
	2	1065 (58.6%)	46 (21.6%)	76 (34.7%)	24 (46.2%)			
	3	405 (22.3%)	69 (32.4%)	84 (38.4%)	18 (34.6%)			
	4-5	107 (5.9%)	87 (40.8%)	51 (23.3%)	7 (13.5%)			
SVI	No	1728 (96.3%)	144 (68.6%)	175 (82.5%)	47 (95.9%)	0.883	<0.001	0.018
	Yes	66 (3.7%)	66 (31.4%)	37 (17.5%)	2 (4.1%)			
EPE	No	1291 (71.2%)	65 (30.5%)	95 (43.4%)	34 (65.4%)	0.365	<0.001	0.004

	Yes	523 (28.8%)	148 (69.5%)	124 (56.6%)	18 (34.6%)			
Pathological margin	Negative	1508 (83.0%)	102 (47.9%)	124 (56.6%)	42 (80.8%)	0.674	<0.001	0.001
	Positive	309 (17.0%)	111 (52.1%)	95 (43.4%)	10 (19.2%)			
Tumour Volume	Median	2.1	5.9	3.5	2.7	0.316	<0.001	0.002
	IQR	1.0-4.0	2.4-11.3	1.8-6.3	1.5-4.7			
PSA Doubling Time	Median	-	9.9	13.5	18.5	-	0.752	0.321
	IQR	-	4.4-20.3	6.8-21.8	13.4-35.0			
PSA Doubling Time Group	<3 mths	-	83 (46.9%)	18 (11.3%)	2 (4.7%)	-	<0.001	<0.001
	3-6 mths	-	25 (14.1%)	29 (18.2%)	0 (0.0%)	-		
	6-9 mths	-	12 (6.8%)	20 (12.6%)	2 (4.7%)	-		
	9-12 mths	-	10 (5.6%)	12 (7.5%)	4 (9.3%)	-		
	>12 mths	-	47 (26.6%)	80 (50.3%)	35 (81.4%)	-		

Table 2. Clinical and pathological characteristics of study cohort categorized by recurrence groups. cT = clinical T-stage; pT = pathological T-stage; EPE = extraprostatic extension; SVI = seminal vesicle invasion.

Recurrence Group		No recurrence	>60 months	p-value (>60mths vs no recurrence)
n = 446		394 (88.3%)	52 (11.7%)	
Age	Median	61	62	0.451
	IQR	57-65	57-65	
PSA	Median	6.1	6.5	0.143
	IQR	4.9-8.3	5.4-9.0	
cT	1	297 (75.4%)	28 (53.8%)	0.001
	2	96 (24.4%)	22 (42.3%)	
	3	1 (0.3%)	2 (3.8%)	
Biopsy Gleason Sum	≤6	156 (39.6%)	10 (19.2%)	0.001
	7	214 (54.3%)	34 (65.4%)	
	≥8	24 (6.1%)	8 (15.4%)	
Biopsy ISUP Grade Group	1	156 (39.6%)	10 (19.2%)	<0.001
	2	166 (42.1%)	19 (36.5%)	
	3	48 (12.2%)	15 (28.8%)	
	4-5	24 (6.1%)	8 (15.4%)	
pT	2	317 (80.5%)	34 (65.4%)	0.013
	3	77 (19.5%)	18 (34.6%)	
Prostatectomy Gleason Sum	≤6	75 (19.0%)	3 (5.8%)	0.001
	7	304 (77.2%)	42 (80.8%)	
	≥8	15 (3.8%)	7 (13.5%)	
Prostatectomy ISUP Grade Group	1	75 (19.0%)	3 (5.8%)	<0.001
	2	228 (57.9%)	24 (46.2%)	
	3	76 (19.3%)	18 (34.6%)	
	4-5	15 (3.8%)	7 (13.5%)	
SVI	No	370 (97.6%)	47 (95.9%)	0.478
	Yes	9 (2.4%)	2 (4.1%)	
EPE	No	313 (79.4%)	34 (65.4%)	0.022
	Yes	81 (20.6%)	18 (34.6%)	
Pathological margin	Negative	335 (85.0%)	42 (80.8%)	0.426
	Positive	59 (15.0%)	10 (19.2%)	
Tumour Volume	Median	1.9	2.7	0.032
	IQR	0.8-3.3	1.5-4.7	
PSA Doubling Time	Median	-	18.5	-
	IQR	-	13.4-35.0	-
PSA Doubling Time	<3 mths	-	2 (4.7%)	-

Group	3-6 mths	-	0 (0.0%)	-
	6-9 mths	-	2 (4.7%)	-
	9-12 mths	-	4 (9.3%)	-
	>12 mths	-	35 (81.4%)	-

Table 3. Clinical and pathological characteristics of patients with greater than 60 months of follow up.

cT = clinical T-stage; pT = pathological T-stage; EPE = extraprostatic extension; SVI = seminal vesicle invasion.

Logistic Regression – No Recurrence vs. Late

	OR	95% CIs	p-value
Age	0.99	0.94 – 1.03	0.55
PSA	1.04	0.99 – 1.09	0.15
pT	1.57	0.80 – 3.07	0.19
Prostatectomy ISUP Grade Group	2.14	1.43 – 3.20	<0.001
Positive pathological margin	1.05	0.48 – 2.30	0.90

Table 4. Summary of Logistic Regression analysis of predictors comparing no recurrence to late (>60 months) biochemical recurrence in patients with greater than 60 months of follow up. PSA = Prostate-specific antigen; pT = pathological T-stage.

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