Original Article

Increased prostate cancer specific mortality following radical prostatectomy in men presenting with voiding symptoms—A whole of population study

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A B S T R A C T

Background: Whole of population studies reporting long-term outcomes following radical prostatectomy (RP) are scarce. We aimed to evaluate the long-term outcomes in men with prostate cancer (PC) treated with RP in a whole of population cohort. A secondary objective was to evaluate the influence of mode of presentation on PC specific mortality (PCSM).
Methods: A prospective database of all cases of RP performed in Victoria, Australia between 1995 and 2000 was established within the Victorian Cancer Registry. Specimen histopathology reports and prostate-specific antigen (PSA) values were obtained by record linkage to pathology laboratories. Mode of presentation was recorded as either PSA screened (PSA testing offered in absence of voiding symptoms) or symptomatic (diagnosis of PC following presentation with voiding symptoms). Multivariate Cox and competing risk regression models were fitted to analyze all-cause mortality, biochemical recurrence, and PCSM.
Results: Between 1995 and 2000, 2,154 men underwent RP in Victoria. During median follow up of 10.2 years (range 0.26—13.5 years), 74 men died from PC. In addition to Gleason score and pathological stage, symptomatic presentation was associated with PCSM. After adjusting for stage and PSA, no difference in PCSM was found between men with Gleason score ≤ 6 and Gleason score $3 + 4 = 7$. Men with Gleason score $4 + 3$ had significantly greater cumulative incidence of PCSM compared with men with Gleason score $3 + 4$.
Conclusions: Primary Gleason pattern in Gleason 7 PC is an important prognosticator of survival. Our findings suggest that concomitant voiding symptoms should be considered in the work-up and treatment of PC.

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Introduction

Prostate cancer (PC) is the most commonly diagnosed male malignancy and the second most common cause of cancer-related death in Australia, and its incidence continues to increase in the Asia-Pacific region.[1,2] The use of open radical prostatectomy (RP) for the surgical management of localized PC increased dramatically during the 1990s subsequent to the increasing use of prostate-specific antigen (PSA) testing and improved operative techniques.[3–5] In more recent years, advances in laparoscopic and robotic surgery have seen a significant fall in rates of open surgery for PC.[6] Due to the relatively recent uptake of robotic surgery, long-term survival data following surgery for PC is largely limited to open RP series.

PC is associated with a long natural history. Multiple studies of long-term follow-up data in patients managed with observation and surgery have been published, although few of these represent

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whole of population series.[7–13] Lower PC specific mortality (PCSM) observed in men with more low-risk disease has resulted in a shift towards increased use of active surveillance.[14–16] Conversely, men with higher risk PC may have the greatest survival benefit from surgery, as those with aggressive disease may be cured by RP alone or as part of multimodality treatment.[9,17,18]

Presentation in men with PC is usually asymptomatic and based on serum PSA, however, there is a subgroup of men presenting with lower urinary tract symptoms (LUTS) who potentially harbor a malignancy.[19,20]

In this study, we evaluate the long-term survival outcomes in a prospective whole of population study of men treated with RP in the PSA era. Furthermore, we sought to identify the impact on PCSM of symptomatic presentation with voiding dysfunction leading to cancer diagnosis, as opposed to diagnosis based purely on PSA testing.

Materials and methods

Patient population

The Victorian Radical Prostatectomy Registry is a prospective whole of population series of men who underwent RP for the treatment of clinically localized prostate adenocarcinoma between 1995 and 2000 in Victoria, Australia. This database was established within the Victorian Cancer Registry, which documents all cancer cases in the state, excluding nonmelanoma skin cancer, and is managed by the Cancer Council Victoria. Further details regarding patient registration and data collection have previously been published.[3]

Clinical and histopathological details

The mode of presentation was recorded at registration as either PSA screened (PSA testing offered by a urologist or general practitioner in the absence of significant voiding symptoms), symptomatic, or other. Symptomatic presentation was defined as patients who sought treatment for irritative or obstructive symptoms and were subsequently diagnosed with PC. Specimen histopathology reports, and pre- and post-RP PSA surveillance values were obtained by record linkage to pathology laboratories. Biochemical recurrence (BCR) post-RP was defined as two consecutive PSA values ≥ 0.2 ng/mL and the latter date taken as the time of recurrence. Deaths were recorded by the Victorian Cancer Registry as either death from PC, death from another cancer, or death from another cause. Men who received neoadjuvant therapy were excluded from all analyses.

Statistical analysis

Multivariate Cox proportional hazards models were fitted to analyze all-cause mortality and time to BCR. Competing risks regression based on the Fine and Gray model, with other cause mortality as the competing risk, was fitted to analyze overall PCSM as well as subgroup PCSM and was used to generate cumulative incidence plots. In all regressions, time from surgery was used as the time axis and all covariates were entered into the model simultaneously. Formal statistical testing of the proportional hazards assumption in the Cox models using Schoenfeld residuals found that it was not violated. Proportionality was assessed in the competing risks regression by including interactions with a time variable for all covariates and these were found to be nonsignificant. In the symptomatic subgroup analysis, age at surgery and PSA were found to be not normally distributed by the skewness-kurtosis test and hence were compared with the Wilcoxon rank

sum test. Grade and stage were compared using the Kruskal-Wallis test. All tests were two sided and significance level was set at $P \leq 0.05$.

Analyses were performed using Stata 12.1 SE (Statacorp, College Station, TX, USA).

Results

The full registry comprises 2,154 patients. Baseline characteristics are shown in Table 1. A total of 2,112 individuals had follow-up data available (98.1%). After excluding men who received neoadjuvant therapy, 1,935 individuals had data available including grade, stage, and PSA. These men constitute the population set analyzed in this report. During a median follow up of 10.2 years (range 0.26–13.5 years), 622 men experienced BCR and 233 men died, including 74 from PC.

Results of the multivariate Cox regression analysis used to model risk of BCR, all-cause mortality, and PCSM are shown in Table 2. Increasing Gleason grade and tumor stage were strongly associated with time to BCR and PCSM. The nonsignificant result for pT4 tumors in all-cause mortality was likely due to the small number of events in this series. A higher baseline PSA was associated with reduced time to BCR, but was not found to be predictive of PCSM or overall mortality. Older age at surgery predicted time to all-cause mortality but not PCSM.

Symptomatic presentation with subsequent diagnosis of PC was significantly associated with older age and higher PSA, grade, and stage as shown in Table 3. After multivariate adjustment of these clinicopathologic parameters, there was still an association between symptomatic presentation and time to PCSM ($P = 0.036$, Fig. 1).

There were 16 PC-specific deaths observed in men who had Gleason score ≤ 6 disease and 14 in men with Gleason score $3 + 4 = 7$ disease. After adjusting for pathological stage, PCSM outcomes for Gleason score ≤ 6 and $3 + 4$ tumors did not significantly differ ($P = 0.231$, Fig. 2). In a low risk subgroup of men with PSA ≤ 10 ng/mL and pT1/T2 stage ($n = 994$, 51.4%), 17 PC deaths were observed overall, including 11 and four men with Gleason score ≤ 6 and $3 + 4$, respectively. Similarly, no significant difference in PCSM was observed between the two groups ($P = 0.649$), although the number of events was small (Fig. 3).

In the subgroup of men with Gleason 7 tumors ($n = 674$), 35 deaths were observed, including 14 and 21 in men with Gleason

Table 1
Baseline characteristics.

	Median (mean)	Range
Age at surgery (yr)	61.9 (61.4)	38.9–81.7
PSA (ng/mL)	8.4 (10.2)	0–112
Gleason grade	*n*	%
2–6	1,123	58.1
7 (3 + 4)	489	25.3
7 (4 + 3)	185	9.6
8–10	135	7.0
Pathological stage	*n*	%
T1/T2	1,437	74.4
T3a	294	15.2
T3b	160	8.3
T4	41	2.1
Mode of presentation	*n*	%
Symptomatic	631	32.7
Nonsymptomatic	1,301	67.3
Urologist	(206)	(15.8)
GP screen	(1,095)	(84.2)

GP, general practitioner; PSA, prostate-specific antigen.

Table 2
Multivariate cox regression analysis.

	Biochemical recurrence			All-cause mortality			Prostate cancer-specific mortality		
	n	HR (95% CI)	*P*	*n*	HR (95% CI)	*P*	*n*	HR (95% CI)	*P*
Baseline characteristics									
Symptomatic (vs. not)	215	1.06 (0.90−1.25)	0.481	101	1.34 (1.03−1.74)	0.029	37	1.64 (1.04−2.60)	0.034
Age (yr)	−	1.00 (0.99−1.01)	0.997	−	1.07 (1.04−1.09)	< 0.001	−	0.99 (0.95−1.03)	0.514
PSA (per 5 ng/mL)	−	1.09 (1.05−1.12)	< 0.001	−	1.01 (0.94−1.07)	0.862	−	1.00 (0.90−1.10)	0.950
Gleason score									
≤ 6 (reference group)	245	−	−	104	−	−	16	−	−
7 (3 + 4)	203	1.90 (1.57−2.30)	< 0.001	52	1.08 (0.77−1.52)	0.665	14	1.61 (0.79−3.30)	0.194
7 (4 + 3)	96	2.34 (1.83−3.01)	< 0.001	37	1.72 (1.15−2.58)	0.008	21	4.75 (2.45−9.22)	< 0.001
8−10	78	2.24 (1.69−2.98)	< 0.001	40	2.36 (1.55−3.60)	< 0.001	23	5.39 (2.61−11.11)	< 0.001
Pathological stage									
T1/T2 (reference group)	369	−	−	139	−	−	23	−	−
T3a	123	1.35 (1.09−1.67)	0.006	38	1.15 (0.79−1.66)	0.478	16	2.37 (1.23−4.55)	0.010
T3b	107	2.36 (1.86−2.98)	< 0.001	49	2.25 (1.54−3.30)	< 0.001	31	5.83 (3.18−10.69)	< 0.001
T4	23	2.03 (1.29−3.19)	0.002	7	1.58 (0.73−3.42)	0.245	4	5.15 (1.88−14.06)	0.001

CI, confidence interval, HR, hazard ratio; PSA, prostate-specific antigen; SHR, subhazard ratio.

Table 3
Comparison of symptomatic versus nonsymptomatic men.

	Symptomatic Median (mean)	Nonsymptomatic Median (mean)	*P* (for difference)
Age (yr), median (mean)	62.78 (62.09)	61.66 (61.06)	< 0.001
PSA (ng/mL), median (mean)	7.9 (10.36)	8.2 (10.19)	0.017
Gleason Score			
≤ 6 (reference group)	374 (59.3)	749 (57.6)	0.038
7 (3 + 4)	138 (21.9)	351 (27.0)	−
7 (4 + 3)	65 (10.3)	120 (9.2)	−
8−10	54 (8.6%)	81 (6.2)	−
Pathological stage			
T1/T2 (reference group)	455 (72.1)	982 (75.5)	0.023
T3a	91 (14.4)	203 (15.6)	−
T3b	68 (10.8)	92 (7.1)	−
T4	17 (2.7)	24 (1.8)	−

Data are presented as *n* (%) unless otherwise indicated.
PSA, prostate-specific antigen.

score 3 + 4 and 4 + 3 disease, respectively. Men with Gleason 7 disease and primary pattern 4 had significantly greater cumulative incidence of PCSM compared with men with Gleason 7 disease and primary pattern 3, as shown in Fig. 4 (subhazard ratio = 2.79, 95% confidence interval 1.40−5.54, *P* = 0.003).

Discussion

This study represents the largest reported whole of population cohort of men treated with RP with >10-years follow up. Although evaluating the role of screening was not a primary endpoint in this study, we found that in addition to previously demonstrated pathologic predictors of PCSM, mode of presentation influenced survival outcomes. We report a difference in survival between men who were diagnosed with PC following PSA testing offered by their family doctor or urologist, compared with men who had diagnosis of PC made following a presentation with symptoms of urinary obstruction.

Symptomatic presentation was associated with older age and higher PSA, grade, and stage, however, even after adjustment for
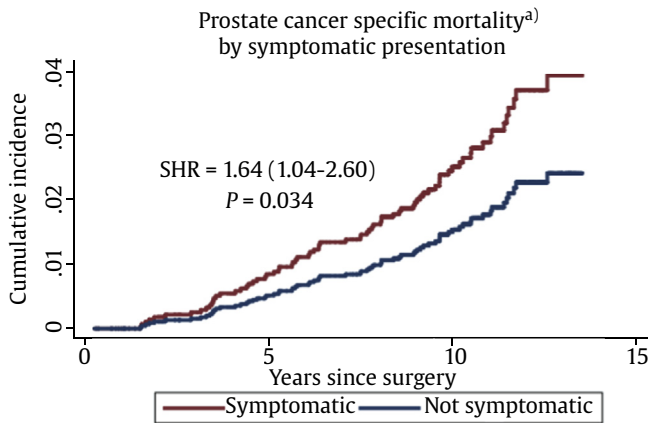

Fig. 1. Symptomatic presentation and prostate cancer-specific mortality. [a] After adjustment for age, PSA, grade and stage. PSA, prostate-specific antigen; SHR, subhazard ratio.
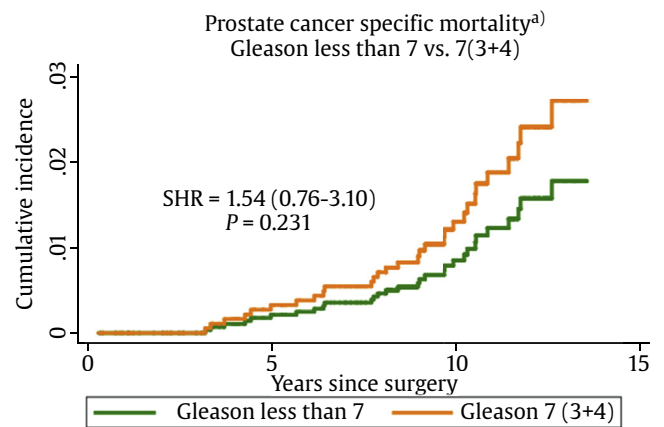

Fig. 2. Comparison of Gleason score ≤ 6 and 7 (3 + 4). [a] After adjustment for stage. SHR, subhazard ratio.

Prostate cancer specific mortality
Gleason less than 7 vs. 7(3+4) in low risk tumours
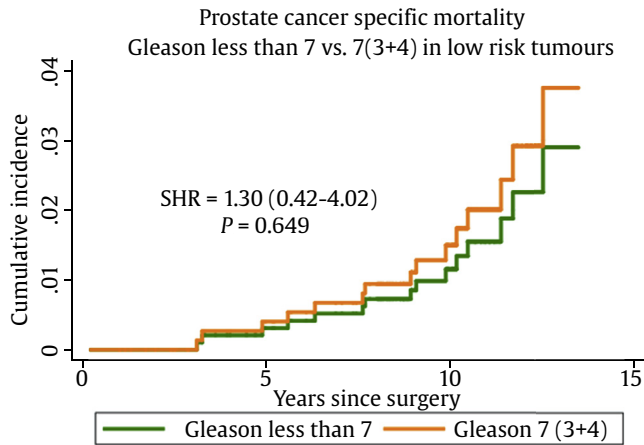
SHR = 1.30 (0.42–4.02)
P = 0.649

Fig. 3. Prostate cancer specific mortality (PCSM) in lower risk prostate cancer (Gleason score ≤ 3 + 4, PSA ≤ 10, pT1/2). PSA, prostate-specific antigen; SHR, subhazard ratio.

these parameters, there was an association between symptomatic presentation and reduced time to PCSM. Minimal data studying this parameter has been published to date, possibly because this variable is less commonly noted now that most PC is PSA detected in North America and Europe. Data from The Swedish National Prostate Cancer Register has shown that most men with PC diagnosed after a health check-up, compared with men presenting with LUTS, have localized tumors of low or intermediate risk.[20] Lee et al[19] found that men with preoperative LUTS as demonstrated by International Prostate Symptoms Score > 8 had a higher incidence of pathologic pT3a disease at the time of RP compared with men with no LUTS.

A possible explanation for this finding may be prostate volume, as men with larger prostates are more likely to experience LUTS. However, data regarding prostate volume was not available for all patients in our study. Although a relationship between prostate volume and symptomatic presentation may exist based on our data, other factors may exist, such as PC arising from the transition zone. This requires further study. Nonetheless, our data suggest that men who present with voiding symptoms should be counseled about PSA testing as part of their work-up of BPH, as some of these men may harbor more aggressive PC.

A further notable finding was the good prognosis of the subgroup of men with Gleason score 3 + 4 PC, especially those with

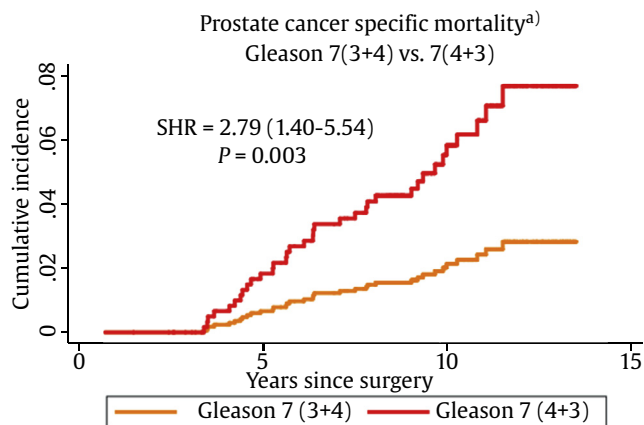Prostate cancer specific mortality[a]
Gleason 7(3+4) vs. 7(4+3)

SHR = 2.79 (1.40–5.54)
P = 0.003

Fig. 4. Effect of primary pattern on prostate cancer specific mortality (PCSM) in Gleason 7 prostate cancer. [a] After adjustment for stage. SHR, subhazard ratio.

low-risk features such as PSA ≤ 10 ng/mL and organ-confined disease. These men had no increased risk of PCSM compared with men with Gleason score ≤ 6. This suggests that in low-volume PC treated with RP, secondary Gleason pattern 4 confers little increased risk of mortality.

Part of this lack of variance in outcomes between Gleason score ≤ 6 and Gleason score 3 + 4 PC in this series where all men were treated by RP may be that although the number of PC-related deaths in both groups was small, the crude mortality rate from Gleason score ≤ 6 disease was higher than expected. In the subgroup of men with Gleason score ≤ 6, PSA ≤ 10 ng/mL, and organ-confined disease, 11 deaths from PC were observed. This observation may be partly explained by the multicenter study design whereby deaths were coded by a centralized cancer registry based on information from death certificates rather than medical records, and it is possible, but unlikely, that a greater proportion of deaths may have been overattributed to PC. Furthermore, prior to the modification of the Gleason scoring system by the International Society of Urological Pathology in 2005, it is possible that some of the Gleason ≤ 6 tumors may have represented Gleason 7 tumors.[21,22]

We found that the subgroup of men with Gleason 7 PC had heterogeneous outcomes. It has been previously shown that primary Gleason pattern 4 in men with Gleason 7 PC is associated with greater BCR following surgery compared with primary Gleason score 3.[23–26] However, the effect of primary Gleason pattern 4 on mortality outcomes in these men is less clear. Among men with Gleason 3 + 4 and 4 + 3 PC, Eggener et al[10] found no difference in 15-year PCSM in >20,000 men treated with RP at multiple large US institutions. Conversely, Wright et al[27] demonstrated higher rates of BCR and PCSM in men with Gleason score 4 + 3 compared with men with Gleason score 3 + 4 in a population-based cohort of men with Gleason 7 PC and median 13-year follow up, although the study was limited to 753 men from a single county under the age of 65 years. Stark et al[28] similarly demonstrated a threefold increase in PCSM in men with Gleason score 4 + 3 compared with men with Gleason score 3 + 4 with 20-year follow up, however, the analysis did not control for PSA or tumor stage. Furthermore, the study was limited to 693 RP specimens and all men were identified from health survey studies conducted on health professionals.

This heterogeneity in outcomes in men with Gleason 7 PC in our study may further be explained by tumor volume. A trend between increasing tumor volume and adverse pathological findings at RP was noted, but was not reported, as tumor volume was not available for all men. It is possible that the presence of primary Gleason pattern 4 is associated with increased tumor volume, and this requires further evaluation. Nonetheless, the distinctions between the predominant Gleason patterns remain important. We confirm in a whole of population setting that amongst men with Gleason 7 PC treated with RP, primary Gleason pattern 4 confers significantly greater PCSM compared with primary Gleason pattern 3.

Some limitations of this study include potentially incomplete data regarding adjuvant or salvage radiation therapy, and an inability to comment on functional or quality of life measures, which are important outcomes following RP. Prostate volume and tumor volume data were also not available for all men. However, this prospective study represents a statewide whole of population register of RP performed by all urologists of varying experience in large tertiary and smaller community hospitals. By including men of varying pathology, socioeconomic status, and residency, and all urologists undertaking RP regardless of their experience or surgical volume, this study is representative of long-term outcomes on a population and community level that may not be reflected in large series from high-volume institutions from the US and Europe.

Conclusion

In this whole of population based study, there appears to be increased PCSM for men treated by RP for clinically localized disease where their presentation was with symptomatic voiding difficulty, in comparison with men who had their cancer diagnosed on the basis of PSA elevation alone. This finding should be considered in determining the most appropriate form of treatment for individual patients, including where active surveillance may be an option. Furthermore, Gleason score $3 + 4 = 7$ PC has been shown in this whole-of-population series to have significantly less PCSM than Gleason score $4 + 3 = 7$ disease, and similar to that of Gleason score 6 disease, reinforcing the significance of this pathologic distinction.

Conflicts of interest

All contributing authors declare no conflicts of interest

Acknowledgments

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