Prostate Int 3 (2015) 75–79

Contents lists available at ScienceDirect

Prostate International

journal homepage: http://p-international.org.

Original Article

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

Anthony D. Ta [1], Nathan P. Papa [1, 2], Nathan Lawrentschuk [1, 3, 4, *], Jeremy L. Millar [5], Rodney Syme [1], Graham G. Giles [2], Damien M. Bolton [1, **]

[1] Department of Surgery, Austin Hospital, University of Melbourne, Melbourne, Australia
[2] Cancer Epidemiology Centre, Cancer Council Victoria, Melbourne, Australia
[3] Olivia Newton-John Cancer Research Institute, Austin Hospital, Melbourne, Australia
[4] Department of Surgical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia
[5] William Buckland Centre, The Alfred Hospital, Melbourne, Australia

ARTICLE INFO

Article history:
Received 26 April 2015
Accepted 4 June 2015
Available online 17 July 2015

Keywords:
Mortality
Prostate tumor
Surgery
Symptomatic
Whole of population

ABSTRACT

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.

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

* Corresponding author.
** Corresponding author. Suite 5, 210 Burgundy St, Heidelberg Vic, 3084, Australia.
E-mail addresses: lawrentschuk@gmail.com (N Lawrentschuk), damienbolton@optusnet.com.au (N Bolton).

http://dx.doi.org/10.1016/j.prnil.2015.06.004

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 $\geq$ 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 $\leq$ 6 disease and 14 in men with Gleason score 3 + 4 = 7 disease. After adjusting for pathological stage, PCSM outcomes for Gleason score $\leq$ 6 and 3 + 4 tumors did not significantly differ ($P = 0.231$, Fig. 2). In a low risk subgroup of men with PSA $\leq$ 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 $\leq$ 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.