

Presenting stage and risk group in men dying of prostate cancer

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ABSTRACT

Introduction Prostate cancer remains the 3rd leading cause of cancer-related mortality in Canadian men, and yet screening for prostate cancer continues to be controversial because the majority of men diagnosed with prostate cancer do not die of the disease. It also remains uncertain whether treatment of cases that can be treated with curative intent alters the mortality rate. There are very few studies describing the presenting stage, risk groups, and survival after diagnosis for men dying of prostate cancer in the literature. In this study, we explored these characteristics for all men who died of prostate cancer in British Columbia between 2013 and 2015.

Methods The population-based BC Cancer databases were used to identify all patients diagnosed between January 2013 and December 2015 who died of prostate cancer. Patient, tumour, and treatment characteristics were collected, and the risk grouping for each tumour was determined. The proportion of cases in each risk group at the time of diagnosis was determined. Survival time from diagnosis to death was calculated for all patients and for each risk group using the Kaplan–Meier method.

Results A total of 1256 patients died of prostate cancer. Of patients who presented with metastatic disease, 57.2% presented with a Gleason score of 8 or more, compared with only 35.7% of patients who presented with nonmetastatic disease ($p < 0.0001$). The presenting stage and risk group of those dying of prostate cancer were as follows: 32% metastatic disease, 3% regional (defined as node-positive), 39% localized high risk, 9% localized intermediate risk, 4% localized low risk, 6% localized not otherwise specified, and 7% unknown. Therefore, 80.3% of those with a known risk group presented with either localized high-risk, regional, or metastatic disease at diagnosis. The median survival times from diagnosis to death were 12 years for localized low-risk, 10 years for localized intermediate-risk, 6.5 years for localized high-risk, 4 years for regional, and 1.7 years for metastatic disease at diagnosis.

Conclusions This population-based analysis demonstrates that patients with localized high-risk, regional, or metastatic disease at diagnosis constitute the overwhelming majority of patients who die of prostate cancer in British Columbia. Unless these disease states can reliably be identified at an earlier low- or intermediate-risk localized state in the future, it is unlikely that treatment of localized low- and intermediate-risk cancer will have an impact on survival. Furthermore, patients with *de novo* metastatic disease had identifiable risk factors of a higher prostate-specific antigen and Gleason score. Further studies are required to confirm these results.

Key Word Death, cancer-related mortality

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INTRODUCTION

Prostate cancer is the leading cancer found in Canadian men, accounting for approximately 20% of new cancer cases¹. Since the early 2000s, the age-standardized incidence has been declining at a rate of 1.6% per year¹. The mortality rate for prostate cancer has also declined in Canada

since the mid-1990s and accounts for only 9.5% of cancer deaths. The role that screening with the prostate-specific antigen (PSA) test has played in the decrease in mortality rate is unclear^{1–3}, in part due to uncertainty about whether mortality is altered by identifying and treating cases that can be identified with screening. Likely due to screening, there has been a shift in the initial staging of prostate

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cancer in Western countries in the last 30 years, whereby the incidence of metastasis at diagnosis has decreased from more than 50% in the 1970s to less than 10% currently⁴⁻⁷.

Despite the observed declines in incidence, mortality, and changes in stage at presentation, prostate cancer remained the 5th leading cause of cancer-related mortality in men in Canada in 2019¹. Although most patients diagnosed with prostate cancer die of other causes, there is conflicting information as to the best way to identify which patients are destined to experience prostate cancer-specific mortality. The stage at presentation and risk groupings, in particular for men dying of prostate cancer, are not well described in the literature. Previous studies suggest that 56% of patients who die of prostate cancer have metastatic disease at diagnosis⁴. Of those presenting with localized disease at diagnosis, 86% had either intermediate- or high-risk disease⁴ (with risk groups defined according to the D'Amico classification⁸). However, this finding is in the context of clinical trials, which are not entirely generalizable to the general population on account of stringent enrolment criteria.

Understanding the risk factors and stage at presentation for men dying of prostate cancer in a population-based setting is relevant to understand how patients present who will succumb to their disease and provide insights into changes that can be made to affect the overall mortality rate.

Thus, the present study explored the characteristics of prostate cancers in patients who died of their disease in British Columbia between 2013 and 2015.

METHODS

Population-based BC Cancer databases were used to identify all patients who died of prostate cancer between January 2013 and December 2015 in the BC Cancer Registry. These patients were linked to the provincial pharmacy database (comprehensive provincial database from 1998 onward), a provincial radiotherapy database (comprehensive from 1984 onward), and databases containing PSA information for men diagnosed with prostate cancer (varied in comprehensiveness over the era of study). Specific inclusion criteria for this study were as follows: British Columbia residency, with a prostate cancer diagnosis as a primary cause of death between 2013 and 2015. Key exclusion criteria included other cancer diagnoses.

A number of patient, tumour, and treatment characteristics were collected, including date of diagnosis, birth, and death; Gleason score; PSA level at diagnosis, radical treatment received at diagnosis, if applicable (for example, external-beam radiation or brachytherapy); date of initiation of androgen deprivation therapy (ADT); and date of initiation of chemotherapy for prostate cancer, which was primarily docetaxel during the study period.

Main risk groupings were localized, regional (defined as node-positive disease), metastatic, and unknown. The localized group was further characterized as low, intermediate, or high risk (using Canadian Consensus risk groupings)⁹, and localized not otherwise specified (NOS).

The proportions of cases in each risk group at the time of diagnosis were determined. Survival time from diagnosis to death was calculated for all patients and for each risk group using the Kaplan–Meier method.

RESULTS

A total of 1256 patients died of prostate cancer during the timeframe of this study. The patient and tumour characteristics, categorized by stage of presenting diagnosis, are shown in Table 1. The median age was not significantly different between patients who presented with versus without metastatic disease ($p < 0.0001$). The median PSA was significantly higher in patients who presented with metastatic disease, compared with those who did not ($p < 0.0001$).

Of patients who presented with metastatic disease, 57.2% presented with a Gleason score of 8 or greater, compared with only 35.7% of patients who presented with nonmetastatic disease ($p < 0.0001$). Only 2 (0.5%) patients with metastatic disease presented with a Gleason score of 6 or less, compared with 84 patients (11.1%) without metastatic disease.

A much higher proportion of patients presenting without than with metastasis received some type of radiation therapy (35.4% vs. 1.7%, $p < 0.0001$), most commonly external-beam radiation therapy (EBRT).

The breakdown by risk group is presented in Figure 1. Using available databases, a full 93% could be categorized into a risk group at diagnosis. Of those with a known risk group, 35% of those dying of prostate cancer presented with metastatic disease at diagnosis, and 80.3% presented with either localized high-risk, regional, or metastatic disease at diagnosis.

Table 2 reflects the outcomes based on the presenting stage of prostate cancer at diagnosis. The time to ADT

TABLE 1 Patient and tumour characteristics by metastasis status at diagnosis (Dx) of prostate cancer

Characteristic	Metastasis		
	Yes (n=407)	No (n=756)	Unknown (n=93)
Age at Dx (years)			
Median	74	71	76
Range	39–96	44–105	53–93
PSA at Dx (ng/mL)			
Median	98	19	11.5
Range	0.6–2000	0.89–2000	0.6–18.3
PSA group at Dx [n (%)]			
0–4 ng/mL	10 (2.5)	18 (2.4)	1 (1.2)
4–10 ng/mL	25 (6.1)	103 (13.6)	4 (4.3)
10–20 ng/mL	36 (8.8)	97 (12.8)	7 (7.5)
>20 ng/mL	290 (71.3)	211 (27.9)	0
Unknown	46 (11.3)	327 (43.3)	81 (87.1)
Gleason score [n (%)]			
≤6	2 (0.5)	84 (11.1)	14 (15.1)
7	27 (6.6)	190 (25.1)	12 (12.9)
≥8	233 (57.2)	270 (35.7)	2 (2.2)
Unknown	145 (35.6)	212 (28.0)	65 (69.9)
Local RT within 1 year of Dx [n (%)]			
External-beam RT	7 (1.7)	257 (34.0)	16 (17.20)
Brachytherapy	0	11 (1.5)	0
None	400 (98.3)	488 (64.6)	77 (82.80)

Dx = diagnosis; PSA = prostate-specific antigen; RT = radiation therapy.

initiation was significantly longer in patients presenting without metastases, and the same was true for time to docetaxel chemotherapy and for initiation of androgen receptor axis-targeted agents. The time to death was predictably shorter in those presenting with metastatic disease.

The median as well as 10-year survival rates by risk group are shown in Figure 2. There was a consistent decline in survival when moving from localized, to regional, to metastatic disease, and from low to high risk within localized disease.

DISCUSSION

The results of our study suggest that the majority of patients (80.3%) who had a prostate cancer-specific mortality

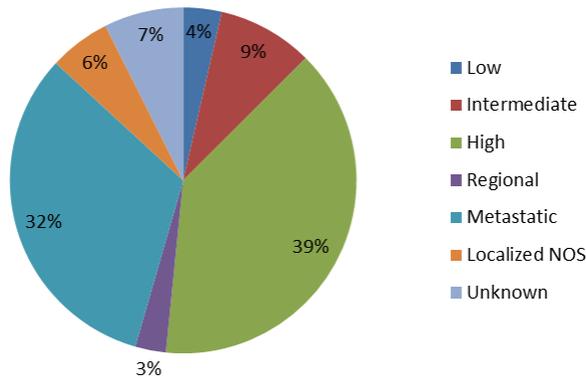
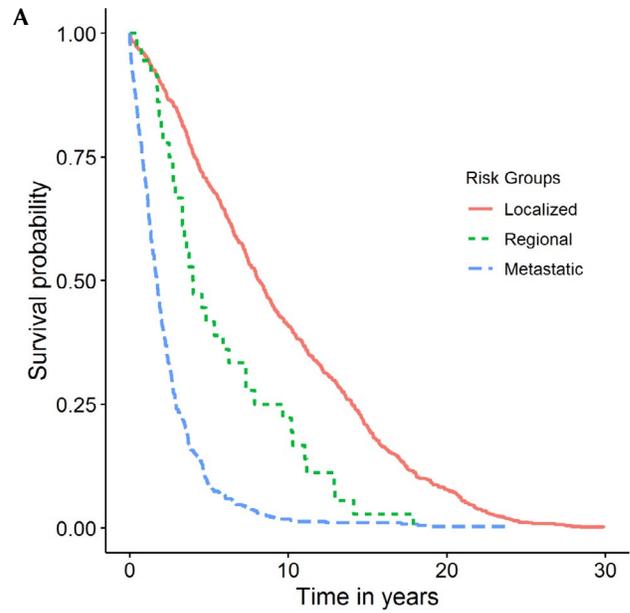


FIGURE 1 Risk groupings of prostate cancer patients who died between 2013 and 2015 (%). NOS = not otherwise specified.

TABLE II Outcomes based on metastasis status at diagnosis (Dx) of prostate cancer

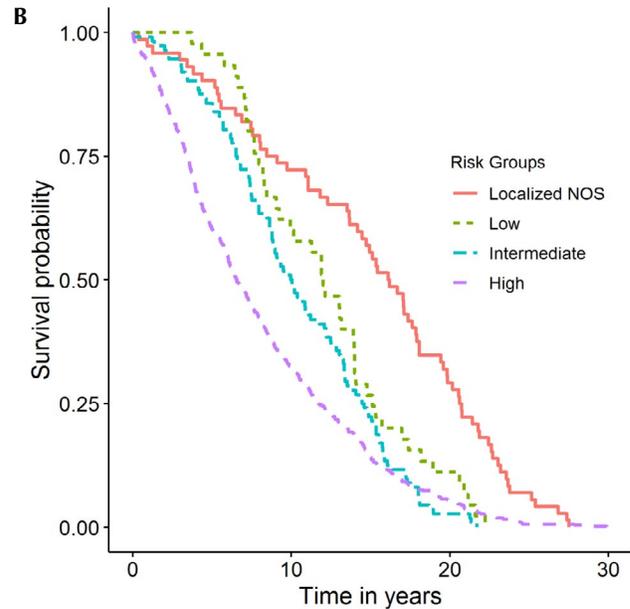
Outcome	Metastasis		
	Yes	No	Unknown
Time to ADT initiation (months)			
Median	0.53	1.25	2.2
Range	0–8.97 (n=365)	0–11.83 (n=478)	0.36–5.88 (n=13)
Time to CTx initiation (months)			
Median	20.17	68.04	151.24
Range	1.25–215 (n=105)	1.87–260.70 (n=169)	96.59–205.90 (n=2)
Time to ARAT agent (months)			
Median	19.33	94.42	181.54
Range	4.04–206.98 (n=142)	3.19–306.66 (n=251)	16.20–324.11 (n=8)
Time to death (months)			
Median	20.80	95.54	135.66
Range	0–285.44 (n=407)	0–358.60 (n=756)	0–413.11 (n=93)

ADT = androgen deprivation therapy; CTx = chemotherapy; ARAT = androgen receptor axis-targeted.



Risk Group	Median Survival (95% CI)	10-year Survival
Localized	8.16 (7.52 - 8.84)	41%
Regional	3.99 (3.32 - 7.32)	22%
Metastatic	1.73 (1.55 - 1.89)	2%

p-value < .0001



Risk Group	Median Survival (95% CI)	10-year Survival
Localized NOS	16.16 (14.18 - 18.07)	72%
Low	12.00 (9.23 - 14.01)	60%
Intermediate	10.00 (8.80 - 12.19)	50%
High	6.56 (6.03 - 7.36)	33%

p-value < .0001

FIGURE 2 Survival of (A) all prostate cancer patients and (B) prostate cancer patients with localized disease who died between 2013 and 2015. CI = confidence interval; NOS = not otherwise specified.

presented with either localized high-risk, regional, or metastatic disease at diagnosis. Furthermore, patients who presented with metastatic disease at diagnosis had a higher PSA at diagnosis, and most had a Gleason score greater than 8. *De novo* metastatic disease also correlated with a shorter time to initiation of ADT and chemotherapy.

This type of population-based analysis is important to help discern how patients present who will go on to die of prostate cancer. This information might allow us to optimally deliver diagnostic procedures, treatments, and interventions to those who need it most, and therefore potentially alter prostate cancer mortality. These findings also imply that, in order to alter the mortality rate from prostate cancer, one either has to shift diagnosis to earlier stages and risk groups through effective screening or develop better treatments of high-risk localized, regional, and metastatic disease. The former mechanism of mortality reduction requires that high-risk localized, regional, and metastatic disease reliably transition through a state of lower-risk localized disease. Given that maturing clinical trials, particularly the relatively uncontaminated European trial, have thus far shown only very modest impacts on prostate cancer mortality and no definite impact on overall survival with PSA screening practices examined, it remains uncertain whether the former mechanism really has the potential for a large impact on mortality reduction.

We have a large body of data now showing us that ADT alone is no longer sufficient for metastatic castration-sensitive prostate cancer. The CHAARTED and STAMPEDE trials first introduced docetaxel to ADT in these patients^{10,11}. Since then, two trials have ushered abiraterone into this disease space^{12,13}, and recently, apalutamide and enzalutamide have shown similar results^{14–16}. We also anticipate results from the phase III PEACE-1 trial (NCT01957436 at <https://ClinicalTrials.gov/>), which combines ADT, local radiotherapy, abiraterone, and docetaxel, as well as the ARASENS trial (NCT02799602), which combines docetaxel and darolutamide. Parker and colleagues have now also recently demonstrated a survival advantage using prostatic radiation for patients with low-burden metastatic castration-sensitive prostate cancer (the “low burden” definition adopted from the CHAARTED trial)¹⁷. Although these trials have demonstrated improvements in survival, none have thus far identified a cure as such. Research in this space is ongoing and will hopefully identify more strategies for improving survival. However, our role must also be to ensure that the treatments get to patients who stand to benefit from them the most.

We report a lower percentage of patients who presented with metastatic disease (32.4%) than in a study by Fizazi and colleagues (55.7%), which looked at 116 patients who died of prostate cancer in clinical trials from 2008 to 2011⁴. This difference might reflect that fact that the Fizazi study was based on cases enrolled in clinical trials at tertiary cancer centres, whereas our trial was population-based. The differences might also reflect differences in screening and staging practices across different countries or a different era of prostate cancer treatment. Nonetheless, both trials underline the point that, although there is only a small incidence of *de novo* metastatic prostate cancer at

diagnosis, these patients contribute a sizeable proportion of prostate cancer-specific deaths.

In patients with localized prostate cancer, those categorized as localized NOS had a greater survival than the other risk groups. While we cannot be certain as to reasons for this, and acknowledge that it could be a random occurrence, we propose the following explanations: the localized NOS cases were more likely to have been diagnoses in the earlier years of this study, when there was less access to data that further characterized them. Therefore, these cases would have had longer follow-up in order for their deaths to have fallen between the dates specified by this study; another possibility is that they were more likely to have been very-low-risk cases that were put on active surveillance and only referred later, at time of progression.

A strength of this study is its population-based nature, which reflects more generalizable results than clinical trials and captures a larger variety of practice patterns. This study also offers a Canadian context to add to the existing literature, where screening and treatment availabilities might differ from those in other countries.

Limitations of this study include the relatively small patient numbers and retrospective nature. These data were also collected at a time before either docetaxel or abiraterone were used upfront in the metastatic castration-sensitive setting, which is now the standard of care, and so the survival outcomes reported might not be reflective of what we would see today, although the overall trends are likely similar. Finally, there were certain data features that we were not able to collect in this study, which would have been useful for analysis. For instance, information on who received a radical prostatectomy could not be collected in a comprehensive way across the entire era. Time to castration resistance was also not available because serial PSA readings were not available through the provincial databases used. It is possible that with more modern staging, particularly with positron-emission tomography (PET) imaging (which was not routinely available during the study period), many of the high-risk localized patients would be re-classified as metastatic or regional at diagnosis.

CONCLUSIONS

This population-based analysis suggests that patients with localized high-risk, regional, or metastatic disease at diagnosis constitute the majority of patients who die of prostate cancer in British Columbia. Furthermore, patients with *de novo* metastatic disease had identifiable risk factors of a higher PSA and Gleason score. Larger studies are required to confirm these results. Future studies examining biomarkers in circulating tumour DNA and circulating tumour cells would be worthwhile to more accurately identify those patients at highest risk of succumbing to their disease. With current stage distributions, treatment interventions directed at low- and intermediate-risk prostate cancer are unlikely to affect prostate cancer mortality in a population. Unless the higher risk and metastatic disease states can reliably be identified at an earlier low- or intermediate-risk localized state in the future, it is unlikely that treatment of localized low- and intermediate-risk cancer will have an impact on survival.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare the following interests: SP reports honoraria from Janssen, Astellas, Bayer, Pfizer, and AstraZeneca; KNC reports grant support, consulting fees, and lecture fees from Janssen, Astellas Pharma, and Sanofi; also grant support and consulting fees from Essa Pharma, Bayer, Pfizer, Roche, and AstraZeneca; TP reports speakers' bureau or honoraria from AbbVie, Sanofi, Servier, Ferring, and Bayer; also consulting fees from AbbVie, Tersera, and Astellas; ST reports speaking events for Bayer and clinical trials for Janssen. The remaining authors have no conflicts to disclose.

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