

# Urological outcomes in nonagenarians with prostate cancer

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## Abstract

**Introduction:** Nonagenarians represent a growing patient population. Herein, we report on the largest cohort of Canadian nonagenarian patients, to our knowledge, with prostate cancer.

**Methods:** A retrospective chart of 44 nonagenarian men diagnosed with localized or metastatic prostate cancer between 2006 and 2019 was performed. Diagnoses were based on pathological specimens or the presence of a high prostate-specific antigen (PSA >20) or abnormal digital rectal exam (DRE) in the setting of metastatic disease on imaging. Patient demographics, presenting complaints, and treatments required were included in the analysis. A descriptive statistical analysis was performed.

**Results:** The median patient age at time of referral was 91.1 years (interquartile range [IQR] 90.2–92.9). The median PSA at time of referral was 54.0 (IQR 18.2–142.6). Metastatic disease was present in 55% of patients at time of diagnosis (n=24). Most patients required at least one urological intervention (n=35). There were 56.8% of patients who received androgen deprivation therapy (ADT) as part of their treatment regime (n=25). Half (50%) of patients were managed with androgen receptor axis-targeted agents (ARAT), as well as ADT (n=22). Five patients (11.4%) underwent surgical castration. Death due to any cause was noted in 52.3% of patients (n=23) throughout the study period, with the median age at death being 94.4 years (IQR 92.3–97.0). Death due to prostate cancer was noted in 18.2% of patients (n=8).

**Conclusions:** This study highlights common presenting complaints for nonagenarian patients with prostate cancer and that many require urological intervention despite advanced age. Future studies should address patient-reported quality-of-life outcomes in the nonagenarian population with prostate cancer.

## Introduction

With modern advances in medicine, physicians and health-care professionals face a unique patient population as life expectancy increases. The life expectancy of Canadians in 2016 was 82.3 years, representing a 15.4% increase since

1960.<sup>1</sup> The nonagenarian and centenarian population are among the fastest growing age groups in Canada and the nonagenarian population is growing steadily worldwide; in 2050, world population projections estimate there will be 76.71 million people aged 90 years or older.<sup>2,3</sup> Prostate cancer is the most common non-cutaneous malignancy in men and its prevalence increases with age.<sup>4</sup> Nonagenarians are largely under-represented within clinical trials and there is a paucity of literature to assist physicians in making clinical decisions regarding their care. In order to provide effective treatment for this emergent patient group, it is important to obtain data about nonagenarians with prostate cancer.

Prostate cancer is generally diagnosed in younger men based on routine prostate-specific antigen (PSA) screening or an abnormal digital rectal exam (DRE) leading to biopsies. Canadian Urological Association (CUA) guidelines suggest limiting prostate cancer screening with PSA to men with a life expectancy of greater than 10 years.<sup>5</sup> The National Comprehensive Cancer Network (NCCN) guidelines endorse observing localized disease in patients with a life expectancy of less than 5–10 years, depending on risk group, and considering palliative androgen deprivation therapy (ADT) with or without radiation for metastatic disease.<sup>6</sup> Clinicians would expect for nonagenarians to be diagnosed more commonly with metastatic disease. Both conservative and palliative treatment options may have significant side effects or result in urological issues that impact quality of life in the nonagenarian population.

This descriptive study aims to assess the interventions and treatment modalities used by urologists in a tertiary care center to manage nonagenarian patients with prostate cancer. We hypothesized that the majority of nonagenarian patients would be managed with observation or palliative ADT. We also hypothesized that there would be a minority of nonagenarians who died of prostate cancer. To the best of our knowledge, this study represents the first reported dataset of Canadian nonagenarian patients with prostate cancer.

## Methods

This project was approved by our local ethics board. The initial nonagenarian database was created by evaluating both inpatient and outpatient referrals made to a urologist at our

tertiary care center between 2006 and 2019. Referrals were identified through billing codes in the electronic medical record (EMR). Patients were included if there was a new diagnosis of prostate cancer as a nonagenarian or if the patient was referred with existing prostate cancer with new or progressive symptoms for management by urology.

Diagnoses were based on pathological specimens or the presence of a high PSA and/or an abnormal DRE in the setting of metastatic disease on imaging. For men diagnosed exclusively on PSA, the inclusion cutoff was 50 ng/ml. If an elevated PSA was in conjunction with physical exam or diagnostic imaging findings consistent with prostate cancer, the PSA cutoff was 20 ng/ml. Patient demographics and comorbidities were included in the analysis, as well as presenting complaints and treatments administered. Comorbidities evaluated included class I comorbidities, as per the Charlson comorbidity index.<sup>7</sup> ADT included luteinizing hormone-releasing hormone (LHRH) agonists and antagonists. Surgical castration was recorded separately. Androgen receptor axis-targeted (ARAT) agents were evaluated separately. Skeletal-related events included: pathological fractures, spinal cord compression, or severe bony pain requiring radiation or surgery to the bone.<sup>8</sup>

Cause of death was determined by evaluating death certificates. Patients with a questionable diagnosis of prostate cancer were excluded from the analytical sample. Medians and interquartile range (IQR) were reported for continuous variables. Frequencies and proportions were reported for categorical variables.

## Results

A retrospective chart review of 44 nonagenarian men diagnosed with localized or metastatic prostate cancer between 2006 and 2019 was performed; 36 of these were outpatient referrals, with eight being inpatient referrals. The median patient age at time of referral was 91.1 years (IQR 90.2–92.9). Just over half (54.5%) of patients presented with metastatic disease (n=24). The most common method of diagnosis was by elevated PSA (n=21). The median PSA at time of referral was 54.0 (IQR 18.2–142.6). The median PSA for patients presenting with metastatic disease was 130.0 (IQR 57.6–322.6). Eight (18.2%) patients were diagnosed by a prostate biopsy; nine (20.5%) patients were diagnosed based off a transurethral resection of the prostate (TURP) specimen. The median PSA for patients diagnosed by prostate biopsy was 35.6 (IQR 16.8–77.3); 75% of the patients who had a prostate biopsy diagnosis had metastatic disease at the time of presentation (n=6). The median PSA for patients diagnosed by TURP specimen was 52.5 (IQR 12.2–73); 44.4% of patients diagnosed by TURP specimen had metastatic disease at the time of presentation (n=4). Two patients were diagnosed on the basis of an abnormal DRE. Almost three-quarters (72.7%) of patients

had one or more class I comorbidities, as per the Charlson comorbidity index (n=32). Coronary artery disease (CAD) was the most common comorbidity identified, found in 56.8% of patients (n=25). Thirteen (29.5%) patients had concurrent malignancy and three (23.1%) of those with concurrent malignancy had a known history of urothelial carcinoma of the bladder. Twenty-six (59.1%) patients were living independently at the time of referral. A summary of demographic data for the entire cohort can be found in Table 1.

The most common presenting symptom patients experienced was urinary retention, which was defined as urinary retention requiring catheterization, with 63.6% of patients presenting with urinary retention at the time of referral (n=28). Skeletal-related events occurred in 29.5% of patients (n=13), with spinal cord compression occurring in 4.5% (n=2). Both of the patients presenting with spinal cord compression received urgent radiation. A total of 43.2% of patients presented with gross hematuria (n=19), although only 13.6% of patients received an evacuation of clots (EoC, n=6). Only two of the patients who received an EoC required a blood transfusion, while 13.6% of the entire cohort required at least one blood transfusion during their treatment course (n=6). The overwhelming majority of patients required at least one urological intervention (n=35). Cystoscopy and catheter insertion were the most common interventions required at 72.7% (n=32) and 75.0%, respec-

**Table 1. Baseline characteristics**

Variables	Overall
Age of referral (yrs)	
Median (IQR)	91.1 (90.2–92.9)
PSA at time of referral	
Median (IQR)	54.0 (18.2–142.6)
Presentation with metastatic disease, n (%)	
Metastatic	24 (54.5)
Method of diagnosis, n (%)	
PSA	21 (47.7)
TURP	9 (20.5)
Biopsy	8 (18.2)
Imaging	2 (4.5)
DRE	2 (4.5)
Unknown	2 (4.5)
Home environment, n (%)	
Independent living	26 (59.1%)
Non-independent living	18 (40.9%)
Comorbidities, n (%)	
Coronary artery disease	25 (56.8)
Other cancer	13 (29.5)
Dementia	11 (25.0)
Chronic kidney disease	8 (18.2)
Diabetes	8 (18.2)

DRE: digital rectal exam; IQR: interquartile range; PSA: prostate-specific antigen; TURP: transurethral resection of prostate.

**Table 2. Symptoms on presentation to urology and urological procedures performed**

Variables	Overall
Urinary symptoms, n (%)	
Urinary retention	28 (63.6)
Pain	24 (54.5)
Hematuria	19 (43.2)
Skeletal related events	13 (29.5)
Spinal cord compression	2 (4.5)
Urological procedures required, n (%)	
Catheterization	33 (75.0)
Cystoscopy	32 (72.7)
Evacuation of clots	6 (13.6)
TURP	6 (13.6)
Nephrostomy tube	1 (2.3)
Ureteric stent	1 (2.3)

TURP: transurethral resection of prostate.

tively (n=33). Table 2 shows presenting symptoms and urological procedures among the entire cohort.

There were 56.8% of patients who received ADT as part of their treatment regimen (n=25). Half (50%) of patients were managed with ARAT, as well as ADT (n=22). Five (11.4%) patients underwent surgical castration. One patient received docetaxal. Five (25.0%) patients obtained a referral to radiation oncology (n=11) and seven (15.9%) received palliative radiation as a part of their treatment course (n=7). Patients treated with palliative radiation all presented with skeletal-related events. Referral to medical oncology occurred in 18.2% of patients, while 20.5% of patients received a referral to palliative care (n=9). Table 3 shows the treatment modality the patient cohort received for management of prostate cancer.

Twenty-three men (52.5%) died during the study period at a median age of 94.4 years (IQR 92.3–97.0). The median time to death from time of referral was 22.7 months (IQR 10.4–39.1). Eight men (18.2%) died of prostate cancer at a median time to death from referral of 14.1 months (IQR 6.6–21.1). Four of the eight patients who died of prostate cancer received one or both of ADT and ARAT. Six of the eight patients who died of prostate cancer presented with metastatic disease. Of the 24 patients that presented with metastatic disease, 22 received ADT. Fifteen (62.5%) patients with metastatic disease died (n=15). Table 4 shows mortality data on our cohort of nonagenarian patients.

## Discussion

Herein, we describe a cohort of nonagenarian patients with prostate cancer managed at our institution. We found that the majority of nonagenarian patients were diagnosed with prostate cancer due to symptomatic disease, which prompted their referral. The management of nonagenarians without metastatic disease is not controversial, although the manage-

**Table 3. Treatment modality**

Treatment modality used, n (%)	Overall
ADT	25 (56.8)
ARAT	22 (50.0)
Watchful waiting	10 (22.7)
Palliative radiation	7 (15.9)
Bilateral orchiectomy	5 (11.4)
Chemotherapy	1 (2.3)

ADT: androgen deprivation therapy; ARAT: androgen receptor axis-targeted agents.

ment of metastatic disease represents a more challenging setting wherein clinicians must weigh the risks and benefits for treatment. Many of our patients presented with metastatic disease, which helps to explain the large proportion of patients who received ADT. We expect that the number of patients with metastatic disease was likely higher, though was not confirmed with imaging, as clinicians may also forgo staging investigations and presume metastatic disease based on PSA alone. Death due to prostate cancer based on cause of death from the death certificates was low in our cohort, although followup was limited in many of these patients.

Patients presenting with an elevated PSA represented a surprisingly large percentage of our cohort. It is important that none of the PSA referrals were screening PSA tests, and rather patients were experiencing symptoms and a PSA was ordered as part of the workup. As such, it is difficult to determine which proportion of PSA tests would be considered inappropriate. In our center, many patients with metastatic disease are managed through the Advanced Prostate Cancer clinic, which is led by urology. This may help to explain the low number of referrals to medical oncology with the relatively large number of patients being managed with ADT and ARAT.

There were a surprisingly high number of patients who underwent prostate biopsies in our cohort. Some of these patients underwent biopsies as part of qualification for clinical trials. One patient underwent a prostate biopsy, which was ordered by the family physician through interventional radiology with subsequent referral to urology. The rationale for the remaining biopsies was unclear.

The management of organ-confined prostate cancer in nonagenarians is not controversial. The NCCN advocates

**Table 4. Mortality data**

Variables	Overall
Death due to any cause, n (%)	23 (52.3)
Death due to prostate cancer, n (%)	8 (18.2)
Age of death (years)	
Median (IQR)	94.4 (92.3–97.0)
Time from referral to death – all (months)	
Median (IQR)	22.7 (10.4–39.1)
Time from referral to death – prostate (months)	
Median (IQR)	14.1 (6.6–21.1)

IQR: interquartile range.

against the use of ADT in patients with a life expectancy of 5–10 years. In the largest series on octogenarian and nonagenarian patients with organ-confined prostate cancer, Dell'Oglio et al found that the cancer-specific mortality was only 19.7%.<sup>9</sup> They advocate against the use of ADT in those with organ-confined disease, as only 3.1% of men aged 90 and above will live for 10 years.<sup>9</sup> This study, however, did not include patients with metastatic disease, where ADT is a mainstay of treatment.<sup>10</sup>

Metastatic prostate cancer presents a unique and challenging situation for urologists when making decisions for the appropriate care of patients with advanced age, as ADT is not a benign form of treatment. Patient symptoms, baseline function, and life expectancy must be considered. Urologists, however, have been shown to be poor estimators of life expectancy in relation to prostate cancer management.<sup>11</sup> This further adds to the complexity of weighing the risks and benefits of treatment of systemic therapy in the nonagenarian population. None of our patients lived longer than 10 years from the time of referral. Nearly 60% of patients lived independently at the time of referral, indicative of a relatively high level of function. Unfortunately, collective prospective data to evaluate quality-of-life outcomes is unlikely to occur in this patient population. It is important to note that the issue is not that urologists expect prostate cancer to take a distinctive form in the nonagenarian population.

This is a retrospective analysis and therefore limited by an inherent selection bias. All of the patients in our cohort were referred to our tertiary care center, thereby excluding patients managed in the community. Moreover, nearly half of the patients were referred to our Advanced Prostate Cancer clinic, resulting in a referral bias. As such, our patient cohort may have more advanced disease than many nonagenarians with prostate cancer. The natural progression of prostate cancer may in part account for the large proportion of patients presenting with metastatic disease. Recommendations for treatment should not be drawn from our study, as the results are purely descriptive. Another limitation to our study is the size of our cohort. While there were only 44 patients, this represents the largest cohort of nonagenarian patients with prostate cancer in Canada.

## Conclusions

As life expectancy increases, urologists can expect for the number of referrals on patients with advanced age and prostate cancer to increase. Nonagenarian patients with prostate

cancer present with multiple urological complaints, many of which require intervention. Our patients were largely managed with ADT ± ARAT. Future studies assessing patient-reported quality-of-life outcomes in the nonagenarian population with prostate cancer would aid in the determination of optimal management strategies for this unique patient population.

**Competing interests:** Dr. Rendon has been an advisory board member and speakers' bureau member for Abbvie, Amgen, Astellas, AstraZeneca, Bayer, Ferring, Janssen, Pfizer, Roche, and Sanofi; has received grants and/or honoraria from Abbvie, Astellas, Bayer, Ferring, Janssen, and Sanofi; hold investments in Myovant; and has participated in clinical trials supported by Abbvie, Astellas, Bavarian, Bayer, Ferring, Janssen, Myovant, Nordic, and Sanofi. Dr. Cox has been an advisory board member for Abbvie and Allergan. No other author reports any competing personal or financial interests related to this work.

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