# A Population-based Study Comparing Outcomes for Patients With Metastatic Castrate Resistant Prostate Cancer Treated by Urologists or Medical Oncologists With First Line Abiraterone Acetate or Enzalutamide

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**OBJECTIVES** To compare toxicity and all-cause mortality for mCRPC patients receiving first line oral systemic therapy prescribed by medical oncologists and urologists.

**METHODS** Population-based retrospective cohort study of chemotherapy-naïve men aged ≥66 years treated for mCRPC with first-line abiraterone or enzalutamide based on administrative health data (Ontario, Canada, 2012-2017). Primary outcomes were hospitalizations/ER visits for any cause or treatment-related toxicity during first-line mCRPC treatment. Secondary outcome was all-cause mortality. We calculated hazard ratios (HRs) comparing outcomes for different medical specialties using multivariable Cox proportional hazards models.

**RESULTS** Among 3405 mCRPC patients, 2407 (70.7%) received abiraterone and 998 (29.3%) received enzalutamide. 1786 (52.5%) patients visited the ER or were hospitalized. Men treated by medical oncologists had an increased risk of hospitalization/ER visits (HR1.16, 95%CI 1.03-1.31; $P = .02$), toxicity-related visits (HR1.34, 95%CI 1.08-1.69; $P = .01$), and mortality (HR1.16, 95%CI 1.02-1.33; $P = .02$) compared to urologists. Limited information was available, beyond PSA adjustment and prior treatment, on patient disease burden.

**CONCLUSION** We observed fewer hospital visits overall and for treatment-related toxicity for mCRPC patients who were prescribed first line abiraterone or enzalutamide by urologists compared to medical oncologists. These differences may result from higher prostate cancer disease burden in patients managed by medical oncologists, and/or other unmeasured differences in patient management between specialties. UROLOGY 153: 147–155, 2021. © 2021 Elsevier Inc.

In 2004, docetaxel was the first agent to demonstrate a benefit for overall survival (OS) in men with metastatic castrate resistant prostate cancer (mCRPC).[1] Given that chemotherapy with docetaxel was the only life-prolonging treatment before 2010, mCPRC patients who received docetaxel were managed almost exclusively by medical oncologists during this period. When orally-administered androgen receptor-axis targeted (ARAT) agents such as abiraterone acetate plus prednisolone and enzalutamide were subsequently shown to improve OS for patients with mCRPC in the post-chemotherapy setting (2011 and 2012 respectively), these agents were also initially prescribed by medical oncologists.[2,3]

Similar OS benefits have now been found when chemo-naïve mCRPC patients are treated with ARAT agents.[4,5] These findings have shifted the paradigm of management: ARAT agents are now the first line of therapy for mCRPC with minimal or no symptoms[6] and recent data has demonstrated their role in metastatic castration-sensitive prostate cancer (mCSPC).[7-9] As these therapies move earlier and earlier in the treatment algorithm, mCRPC management is increasingly being undertaken by urologists and radiation oncologists.

However, the management of mCRPC patients can be complex, and these medications are associated with

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significant toxicities. Abiraterone can result in fluid overload and electrolyte abnormalities; and enzalutamide can result in fatigue, diarrhoea and risk of seizures. Although the toxicities of these medications are common regardless of specialty, the manner in which they present may differ due to differences in management, follow-up, and/or how patients are counselled during their treatment. To our knowledge, there is no information regarding the outcomes of these patients when they are managed by different specialist prescribers.

We conducted a population-based study of men with mCRPC treated with abiraterone or enzalutamide prior to chemotherapy using administrative health data in Ontario, Canada. We compared the frequency of hospitalizations/emergency room (ER) visits for any cause and treatment-related toxicities during first-line mCRPC treatment and overall survival between patients managed by urologists or medical oncologists. This study will further inform patients and clinicians regarding the expected toxicities, and ER visit/hospital readmission rates in real-world practice.

## MATERIAL AND METHODS

### Study Population

Using ICES linked databases, we performed a population-based retrospective cohort study of all men aged 66 and older who received abiraterone or enzalutamide as first-line (chemotherapy-naïve) treatment for mCRPC between January 1, 2012 and December 31, 2017 in Ontario, Canada. These datasets were linked using unique encoded identifiers and analysed at ICES.

Ontario is the largest province in Canada with a population of 14 million people and medical care is reimbursed through a single, government funded health insurance system (Ontario Health Insurance Plan).

We identified patients with a diagnosis of prostate cancer using the Ontario Cancer Registry (which captures about 93% of prostate cancer diagnoses in Ontario [10]) and selected patients who received abiraterone or enzalutamide using information from the Ontario Drug Benefit (ODB) which provides prescription medications to all citizens over the age of 65. The index date was defined as the date of initiation of abiraterone or enzalutamide. We excluded patients treated with docetaxel or cabazitaxel prior to this index date.

During the study interval, abiraterone or enzalutamide were eligible for provincial formulary coverage only for patients with demonstrable evidence of mCRPC. No other indications for use had been approved for coverage during this time period.

### Exposure

We identified prescriptions for first-line abiraterone (approved in 2014) or enzalutamide (approved in 2015) through the ODB database. As complications occurring long after the cessation of therapy are unlikely to be attributable to the medication itself, we considered the exposure period for each medication to begin on the date of first prescription and continue until the end of the prescription plus a wash-out period (2 weeks for abiraterone, 6 weeks for enzalutamide). This wash-out period has been previously described in an Ontario-based population cohort by Wallis et al. [11] Although the wash-out period was slightly longer for enzalutamide, this should not introduce significant bias as the primary outcome is the comparative effects of prescribers (generally similar ratios of abiraterone and enzalutamide use) and we adjusted for the choice of drug therapy in the multivariable analysis.

Medical specialty of the physician prescribing abiraterone or enzalutamide was obtained by linking prescriber identification number from the ODB with the ICES Physician database and categorized as urologists, medical oncologists (medical oncologist, internal medicine, and hematology), and other physician specialties.

### Outcomes

Our primary outcome was the first of a hospitalization or ER visit (i.e. presentation) for (1) any cause and (2) treatment-related complications that occurred during the drug exposure period defined above. Hospitalizations were captured using the Canadian Institute for Health Information (CIHI) Discharge Abstract Database,[12] and ER visits using the CIHI National Ambulatory Care Reporting System. For treatment-related complications, relevant diagnoses were identified using the most responsible diagnosis field and included cardiovascular events, fluid-electrolytes imbalances, infections, and metabolic complications, based on the adverse events reported from the trials of the study medications as determined by our group previously .[11] All-cause mortality during the entire follow-up period (i.e. not limited to drug exposure period) was the secondary outcome.

### Covariates

We captured information on the patient's age at the index date, year of diagnosis, year of first medication prescription, other previous cancers, prior prostate cancer treatments, comorbidity, socio-economic status, and geographic region of residence. We used the ACG System Aggregated Diagnosis Groups (ADGs, Version 10; with malignancy removed) to measure comorbidity,[13] and expressed this using weighted ADG scores.[14]

Although stage and disease extent at the index date are poorly captured within these databases, prostate specific antigen (PSA) values measured within 3 months of the index date were available for 934 of 3405 patients of the total cohort as a potential surrogate for disease severity. At the time of this study, the Ontario Laboratory Information Systems (OLIS) database included data until September 2015; and PSA values were available for about 70% of patients who started ARAT between 2012 and 2015. The use of bone targeted therapies (denosumab or zoledronic acid) prior to the index date was also considered as an indicator of disease severity in an exploratory analysis.

### Statistical Analysis

We examined the association of the introduction of abiraterone or enzalutamide by urologists versus medical oncologists on ER visits/hospitalizations, and all-cause mortality using the Kaplan Meier product-limit method and Cox proportional hazards modelling, adjusting for the covariates described above. Patients were followed from the date of first-line drug initiation until the first event/death, or they were censored at the end of first-line drug exposure or emigration. Statistical significance was set at $P < .05$ based on a 2-tailed comparison. All analyses were performed using SAS 9.4.

## RESULTS

During the study interval, 4236 men over 66 years of age received first-line treatment with abiraterone or enzalutamide for mCRPC. Of these, 831 (18.9%) men received docetaxel or cabazitaxel before the index date, leaving 3405 men in our final cohort (Supplemental Figure 1). A total of 2407 (70.7%) men received abiraterone and 998 (29.3%) received enzalutamide as

their first mCRPC systemic therapy across all years (and 54% and 46% in the final year of data, respectively); 61.9% of abiraterone and 60.7% of enzalutamide prescriptions were provided by medical oncologists, and 24.8% of abiraterone and 19.5% of enzalutamide prescriptions were provided by urologists. Other physician specialties, such as radiation oncologists and general practice physicians, were combined due to low numbers/events (together accounting for less than 10% of the overall cohort; n=335). Physician specialty was missing for 183 (5.3%) patients who were excluded from survival analyses.

The median age of these men was 79 (IQR 73-84) years with median weighted ADG comorbidity score of 17 (IQR 8-24) (Table 1). Age at index date, prostate cancer stage at diagnosis, income quintile, weighted ADG comorbidity score, and diagnosis of other cancers before prostate cancer were similar in urologist and medical oncologist groups.

Overall, 1403 (41.2%) patients did not receive local prostate cancer treatment prior to starting ARAT. Patients treated by urologists were more likely to have no prior local treatment ($n = 430$, 54.4%) compared to medical oncologists ($n = 810$, 38.6%) as those treated by medical oncologists were substantially more likely to have had radiotherapy only previously (42.7% versus 22.5%, $P < 0.0001$). A total of 712 (20.9%) patients received bone targeted agents (denusomab or zolendronic acid); 23.4% and 19.6% of patients under the care of medical oncologists and urologists, respectively (p=0.0007).

In total, 1786 (52.5%) of patients visited ER or were hospitalized, including 51.8% of patients managed by urologists and 53.4% of those managed by medical oncologists (Table 2). Urinary tract infections (UTI) were the most common reason for presentation, affecting 144 (6.9%) and 40 (5.1%) patients under the care of medical oncologists or urologists respectively. Notably, 57 (1.7%) men visited ER or were hospitalized for myocardial infarction or ischemic heart disease. Within the study period, a total of 1672 (49.1%) men died; 347 (43.9%) for whom a urologist prescribed their first-line drug treatment and 1079 (51.5%) for whom a medical oncologist prescribed their first-line treatment.

Figure 1 shows the Kaplan Meier survival curves for (1) all hospitalizations/ER visits, (2) hospitalizations/ER visits associated with specific medication-related toxicity, and (3) overall mortality by prescribing physician type. Patients treated by medical oncologists showed a higher probability of hospitalization/ER visits for all causes ($P = .0007$), for toxicity-related visits ($P = .03$) and for overall mortality ($P < 0.0001$). Of note, the hazards were not proportional over time for mortality and further examination demonstrated that the higher risk of death in patients treated by medical oncologists was driven by an early effect (limited to the first 150 days after starting ARAT), whereas, the probability of death after that time was similar between providers.

We used Cox PH models to examine the association of prescriber with outcomes while adjusting for potential confounders. A total of 3180 patients with complete data for all covariates were included in multivariable analysis (Table 3). Men treated by medical oncologists had an increased risk of hospitalization/ER visits (HR1.16, 95% CI 1.03-1.31; $P = .02$), toxicity-related hospitalization/ER visits (HR1.34, 95% CI 1.08-1.69; $P = .01$), and any cause death (HR1.16, 95% CI 1.02-1.33; $P = .024$) compared to urologists.

In an attempt to account for potential differences in disease severity of patients between physician groups, we re-ran the multivariable analyses in the subset of patients who had PSA values measured within 3 months of their index date ($n = 934$; Supplemental Table). In this subset, the HR comparing medical oncologist to urologist for hospitalizations/ER visits was 1.10 (95% CI 0.90-1.35) and was reduced slightly to 1.05 (95% CI 0.85-1.28) after adjustment for PSA. The HR comparing medical oncologist to urologist for toxicity-related hospitalizations/ER visits was 1.20 (95% CI 0.83-1.75) and was virtually unchanged after adjustment for PSA (HR1.18, 95% CI 0.82-1.74). The HR comparing medical oncologist to urologist for all-cause death was 1.02 (95% CI 0.85-1.24) and changed to 0.93 (95% CI 0.77-1.12) after adjustment for PSA, though not statistically significant. Natural log-transformed PSA was predictive of hospitalization (HR1.11, 95% CI 1.05-1.18, $P = .0003$) and mortality (HR1.25, 95% CI 1.19-1.31, $P < .0001$). Further adjustment for the receipt of bone-targeted agents had no effect on the HR for prescribers.

## COMMENT

As oral ARAT drugs are adopted as first line therapy for patients with metastatic prostate cancer, the management of these complex patients will increasingly be undertaken by urologists and radiation oncologists, in addition to medical oncologists. Looking forward, this trend is likely to continue as these agents move even more proximally into the non-metastatic CRPC (PROSPER,[15] SPARTAN,[16] and ARAMIS[17] trials) and metastatic CSPC (ENZAMET,[7] LATITUDE,[9] and TITAN[8] trials) space, creating a multitude of treatment pathways and options. However, these medications are associated with significant toxicities; and their frequency, and the way they present, may differ due to differences in patient management or counselling between medical specialties.

In this large post-marketing retrospective study of patients with mCRPC treated with first line enzalutamide or abiraterone, we did not find evidence of an increased risk for overall or toxicity-related hospitalization/ER visits in patients who were prescribed these drugs by urologists compared to medical oncologists. In fact, in our main analysis, treatment by urologists was associated with a lower risk of these outcomes compared to treatment by medical oncologists. This observation may result from a referral bias where medical oncologists are more likely to be referred patients with more complex and greater disease burdens, and/or significant medical comorbidity. It is also possible that differences between specialties in the frequency of patient monitoring, the threshold for starting new therapies, and/or other unmeasured confounders could be partially responsible for these results.

We tried to account for bias by adjusting for a number of potentially important confounders (including age, comorbidity and receipt of surgical or radiation treatment); however, we did not have a measure of disease severity at the time starting treatment (index date) for the whole cohort. Adjustment for PSA (a potential indicator of disease severity), in a subset of patients for which PSA was available, had a small effect on the HRs for provider, and provides some support for the existence of this referral bias.

Nonetheless, in the real world, these patients are likely best managed in a multidisciplinary setting where expertise from medical oncologist, radiation oncologists, urologists,

**Table 1.** Characteristics by physician specialty of prescriber of oral systemic therapy

| | | Prescriber of Oral Systemic Therapy | | | | |
|---|---|---|---|---|---|---|
| Variable | Unit | Overall | Urologist | Medical Oncologist | Other | Missing |
| N | | 3,405 | 791 | 2,096 | 335 | 183 |
| **Age at index date (start of ARAT)** | Mean ± SD | 78.9 ± 7.2 | 79.3 ± 7.2 | 78.9 ± 7.1 | 78.0± 7.3 | 79.2 ± 7.4 |
| | Median (IQR) | 79 (73-84) | 80 (74-85) | 79 (73-84) | 78 (72-84) | 79 (72-86) |
| **First systemic agent** | Abiraterone | 2407 (70.7%) | 596 (75.3%) | 1490 (70.9%) | 211 (63.0%) | 110 (60.1%) |
| | Enzalutamide | 998 (29.35) | 195 (24.7%) | 606 (30.1%) | 124 (37%) | 73 (39.9%) |
| **Income Quintile** | *missing* | 17 (0.5%) | *1 - 5 | 11 (0.5%) | *1 - 5 | *1 - 5 |
| | 1 (low) | 535 (15.7%) | *113 - 117 | 350 (16.7%) | *43 - 47 | *20 - 24 |
| | 2 | 654 (19.2%) | 146 (18.5%) | 396 (18.9%) | 72 (21.5%) | 40 (21.9%) |
| | 3 | 697 (20.5%) | 162 (20.5%) | 434 (20.7%) | 66 (19.7%) | 35 (19.1%) |
| | 4 | 755 (22.2%) | 180 (22.8%) | 456 (21.8%) | 81 (24.2%) | 38 (20.8%) |
| | 5 (high) | 747 (21.9%) | 185 (23.4%) | 449 (21.4%) | 68 (20.3%) | 45 (24.6%) |
| **Rurality** | *missing* | 36 (1.1%) | *1 - 5 | 27 (1.3%) | 6 (1.8%) | *1 - 5 |
| | Rural | 358 (10.5%) | *54 - 58 | 225 (10.7%) | 62 (18.5%) | *10 - 14 |
| | Urban | 3,011 (88.4%) | 732 (92.5%) | 1,844 (88.0%) | 267 (79.7%) | 168 (91.8%) |
| **Weighted ADG Comorbidity Score** | Mean ± SD | 17.39 ± 11.77 | 16.34± 11.08 | 17.80 ± 11.94 | 17.39 ± 12.47 | 17.37 ± 11.13 |
| | Median (IQR) | 17 (8-24) | 17 (7-23) | 17 (8-25) | 16 (7-24) | 17 (8-23) |
| **Diagnosis of other cancers before PC** | | 478 (14.0%) | 111 (14.0%) | 296 (14.1%) | 50 (14.9%) | 21 (11.5%) |
| **Prior prostate cancer treatment** | No prior treatment | 1,403 (41.2%) | 430 (54.4%) | 810 (38.6%) | 99 (29.6%) | 64 (35.0%) |
| | Prostatectomy only | 265 (7.8%) | 89 (11.3%) | *145 - 149 | 14 (4.2%) | *15 - 19 |
| | Radiotherapy only | 1,307 (38.4%) | 178 (22.5%) | 894 (42.7%) | 165 (49.3%) | 70 (38.3%) |
| | Prostatectomy followed by Radiotherapy | 404 (11.9%) | 87 (11.0%) | 234 (11.2%) | 54 (16.1%) | 29 (15.8%) |
| | Radiotherapy followed by Prostatectomy | 16 (0.5%) | *3 - 7 | 8 (0.4%) | *1 - 5 | 0 (0.0%) |
| **PSA value** | No | 2,416 (71.0%) | 516 (65.2%) | 1,488 (71.0%) | 271 (80.9%) | 141 (77.0%) |
| | Yes | 989 (29.0%) | 275 (34.8%) | 608 (29.0%) | 64 (19.1%) | 42 (23.0%) |
| | Median (IQR) | 38 (13-107) | 31 (10-82) | 43 (15-116) | 35 (15-85) | 37 (20-123) |
| **Bone treatment prior to index date** | No | 2,693 (79.1%) | 636 (80.4%) | 1,606 (76.6%) | 302 (90.1%) | 149 (81.4%) |
| | Yes | 712 (20.9%) | 155 (19.6%) | 490 (23.4%) | 33 (9.9%) | 34 (18.6%) |

* n is expressed a range for cells with < 6 observations and to prevent calculation from other cells.

**Table 2.** Outcomes by physician specialty of prescriber of oral systemic therapy

| | | Prescriber of Oral Systemic Therapy | | | |
|---|---|---|---|---|---|
| | Overall | Urologist | Medical Oncologist | Other | Missing |
| | N=3,405 | N=791 | N=2,096 | N=335 | N=183 |
| **Visits (Any cause):** | | | | | |
| Hospitalizations | 1,133 (33.3%) | 245 (31.0%) | 730 (34.8%) | 105 (31.3%) | 53 (29.0%) |
| ER visits | 1,280 (37.6%) | 294 (37.2%) | 800 (38.2%) | 118 (35.2%) | 68 (37.2%) |
| Combination of hospital or ER visits | 1,786 (52.5%) | 410 (51.8%) | 1,119 (53.4%) | 166 (49.6%) | 91 (49.7%) |
| **Toxicity Associated Hospital/ER Visits:** | | | | | |
| Any toxicity | 558 (16.4%) | 115 (14.5%) | 362 (17.3%) | 57 (17.0%) | 24 (13.1%) |
| Seizures | *1 - 5 | 0 (0.0%) | *1 - 5 | 0 (0.0%) | 0 (0.0%) |
| Arrhythmias | 56 (1.6%) | 11 (1.4%) | 36 (1.7%) | * 4 - 8 | *1 - 5 |
| Heart failure | 55 (1.6%) | 9 (1.1%) | 36 (1.7%) | *1 - 5 | *1 - 5 |
| Volume overload | *1 - 5 | *1 - 5 | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Hypokalemia | 12 (0.4%) | *1 - 5 | 8 (0.4%) | *1 - 5 | 0 (0.0%) |
| Hypertension | 27 (0.8%) | * 7 - 11 | 15 (0.7%) | *1 - 5 | 0 (0.0%) |
| MI/ischemic heart disease | 57 (1.7%) | 12 (1.5%) | 37 (1.8%) | *1 - 5 | *1 - 5 |
| Anemia | 33 (1.0%) | 6 (0.8%) | 21 (1.0%) | *1 - 5 | *1 - 5 |
| Urinary tract infection | 204 (6.0%) | 40 (5.1%) | 144 (6.9%) | 14 (4.2%) | 6 (3.3%) |
| Joint pain | 25 (0.7%) | * 5 - 9 | 15 (0.7%) | *1 - 5 | 0 (0.0%) |
| Constipation | 52 (1.5%) | 11 (1.4%) | 33 (1.6%) | * 3 - 7 | *1 - 5 |
| Diabetes / hyperglycemia | 26 (0.8%) | 6 (0.8%) | 17 (0.8%) | *1 - 5 | *1 - 5 |
| Liver disease | *1 - 5 | 0 (0.0%) | *1 - 5 | 0 (0.0%) | 0 (0.0%) |
| Neutropenia | 7 (0.2%) | *1 - 5 | *1 - 5 | 0 (0.0%) | 0 (0.0%) |
| Hematuria | 99 (2.9%) | 23 (2.9%) | 59 (2.8%) | 11 (3.3%) | 6 (3.3%) |
| **Death (All-cause)** | 1,672 (49.1%) | 347 (43.9%) | 1,079 (51.5%) | 151 (45.1%) | 95 (51.9%) |

Abbreviations: ER = emergency department; MI = myocardial infarction
* *n* is expressed a range for cells with < 6 observations and to prevent calculation from other cells

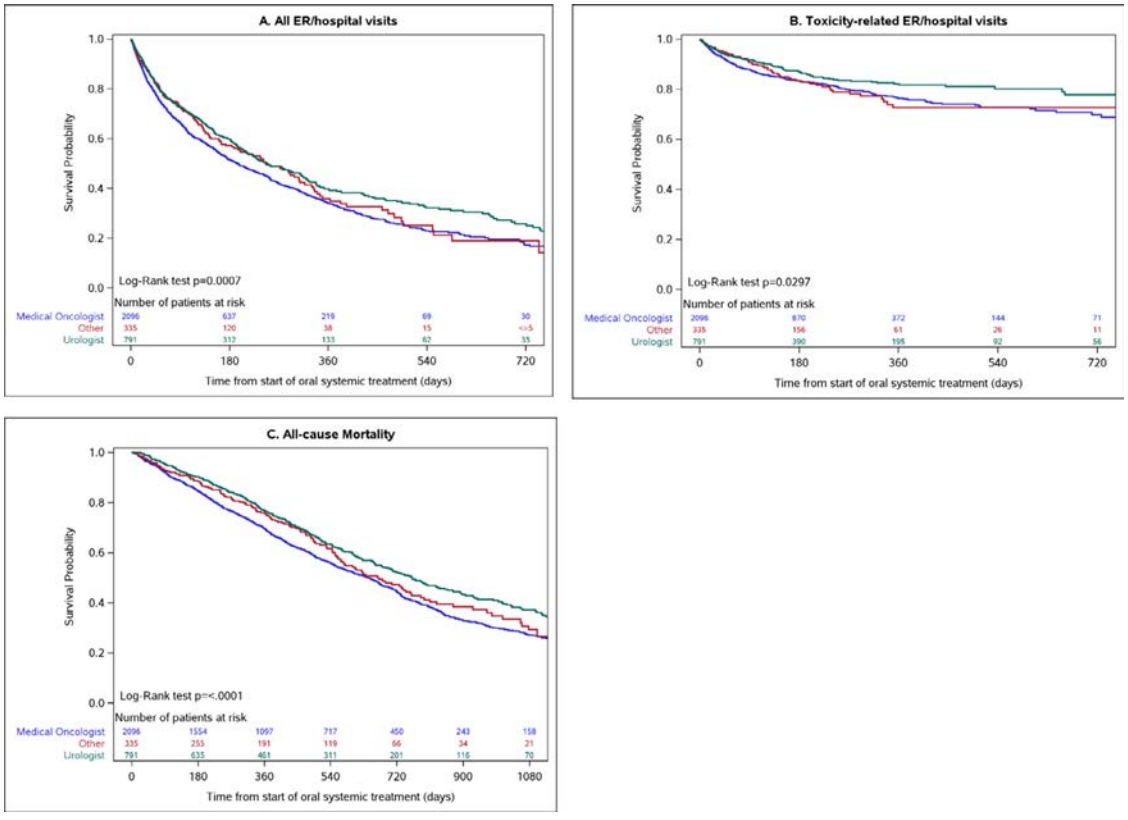


**Figure 1.** Kaplan-Meier curves comparing patients receiving oral systemic therapy managed by urologists, medical oncologists or other medical specialty for the following outcomes: (A) all emergency department visit/hospital admission during drug exposure period; (B) emergency department visit/hospital admission for specific medication-related toxicities during drug exposure period; (C) mortality over entire follow-up period. (Color version available online.)

**Table 3.** Multivariable proportional hazards cox models ($n = 3,180$)

| Covariate | | All Hospital Visits HR (95% CI) | P-Value | Toxicity-related Hospital Visits HR (95% CI) | P- Value | Any Cause Death HR (95% CI) | P- Value |
|---|---|---|---|---|---|---|---|
| **Provider type (ref = Urologist)** | **Medical Oncologist** | 1.16 (1.03, 1.31) | 0.0186 | 1.34 (1.08, 1.69) | 0.0100 | 1.16 (1.02, 1.33) | 0.0240 |
| | **Other** | 1.01 (0.83, 1.23) | 0.9183 | 1.30 (0.91, 1.84) | 0.1448 | 1.10 (0.89, 1.36) | 0.3806 |
| **Oral systemic therapy (ref = Abiraterone)** | **Enzalutamide** | 0.88 (0.78, 1.00) | 0.0524 | 0.88 (0.70, 1.10) | 0.2509 | 0.94 (0.81, 1.08) | 0.3658 |
| **Age (ref = 66-69)** | **70-74** | 1.35 (1.11, 1.66) | 0.0035 | 1.72 (1.17, 2.60) | 0.0073 | 0.97 (0.79, 1.19) | 0.7729 |
| | **75-79** | 1.44 (1.19, 1.75) | 0.0002 | 2.01 (1.39, 2.98) | 0.0003 | 1.08 (0.89, 1.31) | 0.4531 |
| | **80-84** | 1.74 (1.44, 2.11) | <.0001 | 2.00 (1.38, 2.96) | 0.0004 | 1.56 (1.30, 1.89) | <.0001 |
| | **84-89** | 2.09 (1.71, 2.56) | <.0001 | 2.46 (1.68, 3.69) | <.0001 | 1.90 (1.56, 2.32) | <.0001 |
| | **89+** | 2.46 (1.93, 3.13) | <.0001 | 3.20 (2.05, 5.05) | <.0001 | 2.33 (1.81, 2.97) | <.0001 |
| **Year of indexdate (ref = 2012/13)** | **2014** | 0.59 (0.35, 1.12) | 0.0759 | 0.89 (0.33, 3.64) | 0.8426 | 0.78 (0.49, 1.35) | 0.3404 |
| | **2015** | 0.56 (0.33, 1.06) | 0.0525 | 0.88 (0.33, 3.61) | 0.8316 | 0.68 (0.42, 1.18) | 0.1358 |
| | **2016** | 0.53 (0.31, 1.01) | 0.0336 | 0.79 (0.29, 3.23) | 0.6878 | 0.70 (0.43, 1.22) | 0.1760 |
| | **2017** | 0.52 (0.30, 0.99) | 0.0297 | 0.71 (0.26, 2.90) | 0.5561 | 0.63 (0.38, 1.11) | 0.0851 |
| | **2018** | 0.36 (0.19, 0.75) | 0.0042 | 0.34 (0.09, 1.64) | 0.1338 | 0.55 (0.18, 1.43) | 0.2479 |
| **Weighted ADG comorbidity score** | | 1.02 (1.02, 1.03) | <.0001 | 1.03 (1.02, 1.04) | <.0001 | 1.02 (1.02, 1.03) | <.0001 |
| **Income quintile (ref = 5 - high)** | **1 (low)** | 1.16 (0.99, 1.36) | 0.0723 | 0.96 (0.72, 1.27) | 0.7672 | 1.06 (0.90, 1.25) | 0.4888 |
| | **2** | 1.09 (0.94, 1.27) | 0.2640 | 1.01 (0.77, 1.31) | 0.9654 | 1.09 (0.93, 1.28) | 0.2837 |
| | **3** | 1.18 (1.01, 1.37) | 0.0328 | 1.06 (0.82, 1.37) | 0.6630 | 0.92 (0.79, 1.08) | 0.3136 |
| | **4** | 0.96 (0.82, 1.11) | 0.5618 | 0.79 (0.61, 1.04) | 0.0915 | 1.13 (0.97, 1.32) | 0.1175 |
| **Geographic Region**[a] | | | 0.0163 | | 0.0003 | | 0.0623 |
| **Rurality (ref = Urban)** | **Rural** | 1.31 (1.11, 1.55) | 0.0015 | 1.03 (0.77, 1.38) | 0.8226 | 0.95 (0.78, 1.14) | 0.5697 |
| **Any prior prostatectomy treatment** | | 0.87 (0.76, 0.99) | 0.0423 | 0.97 (0.76, 1.21) | 0.7714 | 0.62 (0.53, 0.72) | <.0001 |
| **Any prior radiation treatment** | | 1.20 (1.08, 1.33) | 0.0005 | 1.19 (0.99, 1.42) | | | |

[a] geographic region (represented as 14 Local Health Integration Units) was included in model; however, individual HRs are not shown; *P*-value refers to overall (Type 3) for inclusion of geographic region in the model

and palliative care physicians are available. These are comorbid and complex patients: in our study, about half of mCRPC patients treated with first-line abiraterone or enzalutamide presented to ER or were hospitalized, with the most common toxicity being UTI (similar to postchemotherapy.[11] Further, we observed a median overall survival for the entire cohort of 22 months. Although this is somewhat shorter compared to those from PREVAIL[5] and COU-AA 302,[4] this speaks to the efficacy-effectiveness gap in translating these clinical trials to real-world performance.[18]

The main strengths of this study are the large sample size and the population-based design that captured all hospitalizations, ER visits, and deaths occurring in the province of Ontario. Ontario operates with a single healthcare payer model, allowing for the capture of nearly all patients receiving enzalutamide and abiraterone for this indication, and has been well-described in this population previously.[11] In addition, the study includes physician-specialty stratified data on treatment-related toxicity which are not available in randomized controlled trials.

There are some limitations to our study. First, we only included the first hospitalization or ER visit after the commencement of treatment. Although repeated measures analyses are possible, subsequent events are potentially less attributable to the medication prescriber and may be related to additional confounders (eg, management of the initial event, etc.). Second, although the only approved indication for ARAT during the study period was demonstrated mCRPC, it is possible that these drugs were prescribed for patients at other stages of disease (eg, hormone sensitive disease), and patients may have received mCRPC therapy funded through compassionate use (not captured); however, these situations are likely extremely rare. Third, due to the nonrandomized nature of the study, there may be unmeasured confounders that explain the differences in outcomes between patients managed by urologists and medical oncologists, and which could not be captured by our sensitivity analyses.

## CONCLUSION

Although abiraterone and enzalutamide have been traditionally prescribed by medical oncologists, other specialists are increasingly the primary prescribers of these therapies. In our study, we observed lower toxicity and mortality when patients with mCRPC treated with these medications were managed by urologists compared to medical oncologists. These differences may be a result of higher prostate cancer disease burden in patients managed by medical oncologists, and/or other unmeasured differences in patient management between specialties.


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## FINANCIAL DISCLOSURES

Dr. Wallis reports personal fees from Janssen Canada, outside of the submitted work. Dr. Fleshner reports membership on the advisory boards for Astellas and Janssen, and grants from Astellas, outside of the submitted work. All other authors have nothing to disclose.


## SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2020.11.080.

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## EDITORIAL COMMENT

As treatment options for metastatic castration-resistant prostate cancer (mCRPC) continue to increase, and the timing of optimal treatment shifts earlier in the disease trajectory, the selection and delivery of therapy to patients in the real-world has never been more complex.[1–5] Men with mCRPC are usually older with competing comorbid diseases, frequently have urinary tract complications and bone pain that require coordinated multidisciplinary care, and finally, as is the case with all terminal cancers, have a critical need for establishing realistic goals of care and making end-of-life decisions. With all these factors at play in men with a terminal diagnosis, important questions arise. How do we optimally deliver appropriate therapy for men with mCRPC? Who is prescribing systemic therapies to these patients? And does it matter?

In this issue of *Urology*, Woon et al begin to tackle these questions by utilizing population-level administrative health data to investigate outcomes of men with mCRPC who received first-line abiraterone or enzalutamide in Ontario, Canada. They found that men treated by medical oncologists had slightly increased risk of overall emergency room visits/hospitalizations, toxicity-related visits, and mortality compared to men treated by urologists.

Importantly, the authors draw attention to the fact that unmeasured variables could account for these findings. Perhaps most notable is that there was no data available for several established prognostic factors, including metastatic sites (e.g. visceral or bone), number of metastases, pain, or PSA doubling time, that could distinguish whether patients treated by medical oncologists had a greater disease burden.[6,7] Second, although the specialty of the provider was a tenet of the analysis, characteristics of the practice where the patient is treated could not be accounted for and may significantly influence outcomes. Although the majority of prescriptions (60%) for abiraterone and enzalutamide were written by medical oncologists with only 20%-25% coming from urologists, we don't have information on the types of urologists writing these prescriptions and their practices. If the majority of prescriptions written by urologists were coming from a small subset of practices that may have advanced practice providers and specialty pharmacy involvement with specifically developed plans for the management of men with mCRPC, it is conceivable they may see more men with mCRPC and be more prepared to address complications than some general medical oncology practices.[8–10] Hence, the driving force behind *** et al's findings may be the familiarity, patient volume, and clinical infrastructure available to the provider and less so the provider's specialty.

Although *** et al's findings begin to address whether provider specialty is associated with patient outcomes, a lot of critical questions remain unanswered. What is it about certain providers and the systems in which they practice that drive superior outcomes? If these factors can be better characterized, could they be incorporated into incentives and measures of quality for practitioners and health systems? Treating men with mCRPC is indeed complicated for patients and providers and argues for robust further investigation into how best to deliver their care.

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## AUTHOR REPLY

We appreciate the thoughtful comments by Drs Tsao and Caram et al regarding our manuscript. Our goal was not to claim "superiority" of urology vs medical oncology; but to demonstrate that Urologists' are capable of managing advanced cancer, particularly among patients who are asymptomatic or minimally symptomatic and with agents that possess a low frequency of grade III/IV toxicity. At the end of the day, adverse event rates were equal to or better than published data from an absolute number point of view. We value our medical oncology colleagues greatly and should work with them closely for the best outcomes of our patients. They have true skills that urologists do not have particularly in the utilization of cytotoxic agents and advanced pain management.

As Chairman of an academic program in Urology, I do believe that we cannot pigeon -hole ourselves into only performing technical procedures. We must embrace novel agents in order to manage patients across a host of Urological conditions including oncology. In the future, novel agents including subcutaneously delivered immune-oncology drugs for bladder cancer, HIF-1 alpha inhibitors for Von Hippel Lindau-associated tumors, PARP inhibitors for prostate cancer and in the further future gene editing and DNA-base editing technologies will emerge.

Urology must embrace these therapies, we have always added to the body of scholarly activity in systemic therapy. Access to pharmaceutical companies and their pipelines are integral in for residents, fellows and surgeon scientists- these relationships foster innovation and entrepreneurship. Urology cannot afford to become disconnected from this

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