Practice patterns and predictors of treatment intensification in patients with metastatic castration-sensitive prostate cancer

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ABSTRACT

Introduction: Treatment intensification beyond androgen deprivation therapy (ADT) has shown survival benefit in patients with metastatic castration-sensitive prostate cancer (mCSPC). There is a need to better understand how these novel treatments fit in real-world practice.

Methods: Using electronic medical records and administrative data, a population-based, retrospective cohort study of patients newly diagnosed with de novo mCSPC between 2010 and 2020 in Alberta, Canada, and initiated ADT was conducted. Treatment intensification was defined as the receipt of apalutamide, abiraterone acetate, enzalutamide, or chemotherapy (e.g., docetaxel) within 180 days of ADT initiation.

Results: A total of 2515 de novo mCSPC were identified, with 2098 (83%) patients initiating ADT post-diagnosis. Of those, 525 (25%) received intensification beyond ADT. The percentage of patients who were intensified was 3% in 2010–2013 and gradually increased to 67% in 2020. From 2014–2017, docetaxel was the most commonly used approach, although it was supplanted by abiraterone acetate, apalutamide and enzalutamide from 2018 onwards. In multivariable logistic regression analyses of patients diagnosed from 2014–2020, significant predictors of intensification were younger age at diagnosis, lower Charlson comorbidity index, greater number of metastatic sites, shorter time to ADT initiation, referral to a medical oncologist, transurethral resection of the prostate or radiation prior to ADT, and more recent year of diagnosis (all $p<0.05$). Intensification increased for patients living in rural areas and with higher disease burden in 2018+ compared to 2014–2017.

Conclusions: There has been a considerable increase in the use of ADT intensification therapies that correspond with the timing of clinical trial data and approvals of novel agents.

KEY MESSAGES

- Treatment intensification increased considerably among mCSPC patients over the years from 2014–2020 in Alberta, Canada.
- Younger age, lower Charlson comorbidity index, greater disease burden, prior local treatment and referral to specialists are significant predictors of treatment intensification.
- Use of oral mCSPC agents increased upon their regulatory approval with an observed decrease in docetaxel use.

INTRODUCTION

Prostate cancer is the most common cancer among men and has the third-highest mortality of all cancer types in Canada.[1] Lifelong androgen deprivation therapy (ADT) is standard therapy for metastatic prostate cancer.[2] Unfortunately, regressions in patients with metastatic prostate cancer

are universally transient, with a median duration of disease control between 13 months and 22 months and median overall survival of 28 months to 36 months.[3]

The current Canadian treatment guidelines for metastatic castration-sensitive prostate cancer (mCSPC) recommend ADT plus intensification with either docetaxel, abiraterone acetate, enzalutamide, apalutamide, or triplet therapy if tolerable, but these guidelines have only been present since 2022.[4] Beginning in 2014, the CHAARTED trial showed that treatment with ADT and docetaxel prolongs survival compared with ADT alone.[5] In the LATITUDE trial, the addition of abiraterone acetate plus prednisone to ADT significantly increased overall survival and radiographic progression-free survival for newly diagnosed mCSPC.[6] Recent Phase 3 studies have included patients with low volume disease and show significant clinical benefit of second-generation androgen receptor targeting agents in the broader mCSPC setting. The TITAN study demonstrated that overall survival and radiographic free progression were significantly longer with the addition of apalutamide to ADT for mCSPC.[7] The ENZAMET study reported that enzalutamide produced longer progression-free and overall survival in men with mCSPC receiving ADT.[8]

Given the rapidly evolving landscape in the treatment of mCSPC, there is a need for an improved understanding of how these treatments fit into the historical and current treatment paradigm, and what predicts receipt of those therapies in a real-world setting. Specifically, the objective of this study was to determine how the adoption of treatment intensification has changed over time and predictors of intensification, with the aim to better characterize the patient group who receives ADT monotherapy.

METHODS

Study design and study population

This was a retrospective cohort study that utilized population-level electronic medical records and administrative data from Alberta, Canada. Patients aged ≥18 years who were newly diagnosed with de novo mCSPC between 2010 to 2020 in Alberta and initiated ADT post diagnosis or within 30 days prior. Metastatic prostate cancer cases were identified with the Alberta Cancer Registry (ACR) and ADT was determined through linkage with the Pharmacy Information Network (PIN) database. Patients without evidence of receipt of ADT were excluded. The PIN database was also used to identify mCSPC patients who received treatment intensification with apalutamide, abiraterone, enzalutamide or chemotherapy. Patients who received one of those therapies within 180 days of initiating ADT were considered to have received treatment intensification for mCSPC. Subsequent therapy for progression to mCRPC was defined according to: 1) receipt of a new agent not within the original regimen defined according to the time window from initiation of ADT to 180 days post-ADT; or 2) a gap of more than 180 days between successive dispensations of a non-ADT therapy (gap is from dispensation plus days dispensed and the next dispensation). This study was approved by the Health Research Ethics Board of Alberta – Cancer Committee (HREBA.CC-22-0013).

Study measures

The study measures included were baseline patient and clinical characteristics, treatment uptake, and treatment sequence patterns. Baseline patient and clinical characteristics included were age at diagnosis, rural residence, census level socioeconomic measures (average neighbourhood household income and neighbourhood high school educational attainment), indicators of health in the year prior to diagnosis (emergency room visits and hospitalizations, practitioner claims, and Charlson comorbidity index), number of metastatic sites (i.e. bone would count as one site, even if multiple lesions), referral to a medical oncologist, time to ADT, surgery (transurethral resection of the prostate (TURP)), radiation, and year of diagnosis with mCSPC. While we were able to capture referrals to medical oncology we were not able to include referrals to and treatment by the small number of urologic oncologists in the province who are actively intensifying patients with mCSPC. Receipt of treatment intensification and ADT alone were reported overall and by year of diagnosis. Subsequent therapy for progression to mCRPC were reported.

Statistical analysis

Baseline characteristics and treatment patterns were summarized using the median (interquartile range) for continuous variables and frequency counts (percentages) for categorical variables. All frequency counts with fewer than 10 patients were suppressed due to data privacy regulations. Sankey diagrams were generated to depict the relative sample sizes and proportions of patients receiving different therapies along the treatment trajectory from mCSPC to 1L mCRPC and 2L mCRPC for different eras of treatment intensification (mCSPC diagnosis in 2014-2017 vs. 2018-2020). Multivariable logistic regression was used to determine the association of patient and clinical characteristics with receiving treatment intensification. Continuous variables were categorized to facilitate clinical interpretation and examination of the shape of the association. Multivariable analyses were conducted overall and for different eras of treatment intensification (mCSPC diagnosis in 2014-2017 vs. 2018-2020). To further identify subgroups of individuals who have a high probability of receiving ADT alone versus treatment intensification we conducted a Classification and Regression Tree (CART) analysis. Using the same variables as our multivariable model, we grew a complex tree up to a depth of 30 with a minimum node split size of 2 and a minimum bucket size of 1 with no constraints on the cost-complexity parameter. The resulting tree was pruned according to the cost-complexity parameter that minimized the leave one out cross-validated error rate.

RESULTS

Cohort description

A total of 2515 patients were diagnosed with de novo metastatic prostate cancer in Alberta and there was evidence that 2188 initiated ADT post diagnosis or within 30 days prior (Figure 1). Among patients diagnosed from 2010 to 2013 and who initiated ADT, only 17 (2.4%) received treatment intensification. Given that treatment intensification was rare during this time period

and neither approved nor recommended on the basis of randomized data, subsequent analyses focused on patients diagnosed with metastatic prostate cancer from 2014 to 2020 (n = 1576). Among patients diagnosed between 2014 and 2020, the median age at diagnosis was 74.0 (IQR: 66.0-82.0) and the majority of patients resided in an urban area (69.8%). Of these patients, 27.4% had metastases at multiple sites, 58.6% had at least one ER visit or hospitalization in the year prior to diagnosis, 34.3% had at least one comorbidity, and 37.8% were not referred to a medical oncologist.

Treatment patterns

Of the 1576 de novo mCSPC patients, 545 (34.6%) received treatment intensification and 1031 (65.4%) received ADT alone. The proportion of mCSPC patients who received treatment with ADT alone decreased significantly from 2014 to 2020 (80.6% vs. 38.4%; p-value < 0.001; Table 1). For patients diagnosed from 2014 to 2017, the primary form of treatment intensification was ADT plus docetaxel. The proportion of patients who received docetaxel decreased considerably for patients diagnosed between 2018 and 2020, with increased use of abiraterone acetate in 2018 and 2019 and apalutamide in 2020 (Table 1). Figure 2 displays the sequencing of therapies from mCSPC to mCRPC for patients diagnosed 2014-2017 (Figure 2A) and 2018+ (Figure 2B). For patient diagnosed in 2014-2017, 48.9% received therapy for mCRPC with a considerably higher proportion of the treatment intensification group receiving this treatment compared to the ADT alone group (70.5% vs. 42.9%). A higher proportion of the treatment intensification group also initiated second-line therapy for mCRPC (44.2% vs. 17.7%). For patients diagnosed 2018+, a similar proportion of the ADT alone group and the intensification group received therapy for mCRPC (28.5% vs. 28.7%). The most common mCRPC therapies in 2014-2017 were abiraterone and enzalutamide, while for the 2018+ period abiraterone and enzalutamide were common among the ADT alone group, but docetaxel was the most common among patients intensified.

Predictors of treatment intensification

The crude and adjusted ORs for variables associated with receipt of treatment intensification for mCSPC are shown in Table 2. Compared to mCSPC patients diagnosed in 2014, patients diagnosed in 2018 (OR: 3.10; 95% CI: 1.82-5.35), 2019 (OR: 5.69; 95% CI: 3.27-10.06), and 2020 (OR: 14.23; 95% CI: 7.85-26.42) had significantly higher adjusted odds of receiving treatment intensification. Older age at diagnosis, multiple comorbidities, and a metastasis at only one site were all significantly associated with a lower odds of receiving treatment intensification (Table 2). Referral to a medical oncologist, shorter time to ADT initiation, receipt of TURP prior to ADT, and receipt of radiation prior to ADT were all significantly associated with a higher odds of receiving treatment intensification (Table 2). The crude and adjusted ORs of variables not significantly associated with treatment intensification are displayed in Supplemental Table 1. The results for predictors of treatment intensification by era are presented in Tables 3 and 4. For patients diagnosed 2014-2017, aged 75+ and living in a rural residence had lower odds of

treatment intensification. Being referred to a medical oncologist, earlier time to ADT and having two metastases were associated with treatment intensification. For patients diagnosed 2018+, living in a rural area was not associated with a lower odds of treatment intensification, and patients with 3+ metastases were far more likely to be intensified than the previous era. Being referred to a medical oncologist, earlier time to ADT, and prior treatment with TURP or radiation were associated with treatment intensification in this era.

The results of the cost-complexity pruning CART analysis is shown in Figure 3. Age (< 75 vs. ≥ 75) and year of diagnosis (after June 2018 vs. prior to June 2018) were identified as the most important predictive factors. Patients aged 75+ years had a low probability of receiving treatment (17%) regardless of year of diagnosis. In contrast, patients aged <75 were more likely to receive treatment intensification and this probability was much higher if the patient was diagnosed after June 2018 compared to before. The OR associated with treatment intensification for patients aged <75 and diagnosed after June 2018 (20.4% of study population) was 6.86 (95% CI: 5.21-9.09) compared to all other mCSPC patients.

DISCUSSION

In this study we examined the real-world uptake of treatment intensification among de novo mCSPC patients in Alberta, Canada and identified several predictors of receiving treatment intensification. First, the utilization of treatment intensification increased considerably from 2014 to 2020, where approximately 62% of patients received treatment intensification in 2020. This increase was most prominent in 2018 to 2020 with the adoption and approval of abiraterone (2018 approval), apalutamide (2019 approval), and enzalutamide (2020 approval) and decreased use of docetaxel. Second, in multivariable analyses young age at diagnosis, having multiple comorbid conditions, having a metastasis at only one site, being referred to a medical oncologist, shorter time to ADT initiation, receipt of TURP prior to ADT, and receipt of radiation prior to ADT were all significantly associated with a higher odds of receiving treatment intensification. In analyses of predictors of treatment intensification by era, we observed that intensification increased for patients living in rural areas and patients with higher burden of disease with the introduction of androgen receptor-pathway-inhibitor (ARPIs). These results indicate increasing adoption of treatment intensification due to the availability of ARPIs, but that a considerable proportion of patients who would benefit from these therapies are not being treated with them, which may have considerable impacts on long-term survival and quality of life of mCSPC patients.

In relation to treatment intensification utilization and types of treatment intensification, our results are consistent with other studies from the United States, Europe, and Canada. Using data from the US Veterans Health Administration database, Freedland et al. showed that treatment intensification with docetaxel and abiraterone increased from 2014 to 2018.[9] Similarly, Heath et al. found an increase in treatment intensification with non-hormonal therapy from 2015 to 2021 using nationwide US data.[10] Physician-reported data on adult mCSPC patients across five European countries (United Kingdom, France, Germany, Spain, and Italy) showed

considerably higher rates of treatment intensification in 2019-2020 compared to 2016-2018, but the types of treatment intensification varied across the countries.[11] In a real-world study of men aged 66 years or older with mCSPC in Ontario, Canada, Wallis et al. reported an increase in use of treatment intensification with abiraterone, but the rate of treatment intensification (16.1%) was considerably lower than observed in this study (34.6%).[12] In a previous population-based study conducted in Alberta, Canada, Karim et al. observed a large increase in treatment intensification to 2019 with a 47% uptake.[13] In our population-based study in Alberta, Canada with an extra year of data, we observed further increases in treatment intensification with 62% of patients diagnosed in 2020 being intensified.

Several previous studies have examined predictors of different types of treatment intensification for mCSPC, but to our knowledge no study has conducted multivariable analyses of potential predictors. Both Wallis et al. and Ryan et al. found that patients who received ADT alone were more likely to be older than patients who received treatment intensification, which is consistent with our study.[12, 14] Freedman et al. observed that patients who received intensification with docetaxel or abiraterone had greater disease burden in terms of higher PSA and metastases, which is consistent with our study where we observed that patients with metastases at multiple sites were more likely to receive treatment intensification.[9] A large study from the US reported that oncologists were much more likely to prescribe treatment intensification compared to urologists, while a study of physician reported data in Europe found that treatment intensification was prescribed at a similar rate between oncologists and urologists.[10, 11] It is important to note that neither of those studies conducted multivariable analyses adjusting for potential confounding factors. However, it is likely that these differences could be due to differences in health care settings between the jurisdictions. In this study we did not examine treatment intensification by type of provider, but we did observe that patients who were referred to a medical oncologist were much more likely to receive treatment intensification than patients who were not after adjustment for patient and disease characteristics. To some degree this may reflect referral bias where only patients who are considered eligible for intensification are likely to be referred whereas those who are not candidates or refuse are not being referred. Unfortunately we were not able to assess referrals to and treatment by the small number of urologic oncologists in the province who are actively intensifying patients with mCSPC but the expectation is that intensification rates would be similar to those for patients referred to medical oncology. Importantly, we also identified that having fewer comorbidities, receiving of TURP prior to ADT, and receiving of radiation prior to ADT were associated with a greater likelihood of receiving treatment intensification. We also observed that intensification increased for patients living in rural areas and patients with higher burden of disease with the introduction of ARPIs, indicating the importance of these new therapies for improving widespread adoption of treatment intensification.

To complement the findings of our multivariable regression analysis, we conducted a CART analysis to better understand predictors of treatment intensification among mCSPC patients. Unlike logistic regression, CART analysis does not assume additivity which more easily

allows for the identification of interactions between variables. In our cost-complexity pruned tree, we found that age and year of diagnosis were the most important predictors of treatment intensification and that the association of age depended on year of diagnosis. Specifically, patients over the age of 75 had a low probability of receiving treatment intensification regardless of year of diagnosis and patients under the age of 75 had a high probability of receiving treatment intensification when diagnosed after June 2018. After June 2018, the most prominent intensification therapies prescribed were androgen receptor-pathway-inhibitor (ARPI) therapies (abiraterone and apalutamide), which aligns with clinical trial data and Health Canada approvals. Despite the emergence of these efficacious therapies, there was no significant increase in treatment intensification among patients aged 75+ years. This lack of use among this patient population could be due to perceived lack of efficacy among older patients, unwilling or medically unfit patients, or is an underserviced patient population who could benefit from treatment with ARPIs. While there have been large increases in the use of treatment intensification for mCSPC patients <75 years of age, a considerable proportion (approximately one third) did not receive treatment intensification despite the demonstrated efficacy and improvements in quality of life. Further research on the reasons for not intensifying therapy among both patient populations is necessary to improve outcomes and quality of life for mCSPC patients.

To our knowledge, this is one of the largest and most up-to-date population-based studies to examine the uptake of treatment intensification and to comprehensively identify predictors of treatment intensification among mCSPC patients. Strengths of this study include quality treatment data, which are routinely captured in electronic medical records, and the identification of mCSPC cases through linkage with the ACR. In addition, since the data represents the entire population of Alberta, the results from this study are generalizable to the province. Importantly, the population-based nature allows for an accurate estimation of the proportion of patients who are not receiving treatment intensification, which is underestimated in referral-based studies.[15]

The limitations of this study should be acknowledged. This study relied upon administrative data that do not capture potentially important clinical covariates, such as high vs. low volume disease, high vs. low risk disease, performance status, or disease recurrence. Since this investigation focused solely on de novo mCSPC patients, the results may not be generalizable to recurrent mCSPC patients. In addition, progression to castration resistant prostate cancer or date of this progression was ascertained using an administrative data algorithm, which may have led to misclassification. We were only able to determine the influence of referrals to medical oncologists and not to other specialists providing intensification. Finally, due to delays in updates in the data used for this study, we were not able to capture more recent treatment intensification therapies and therefore follow-up studies will be required to determine how these new therapies have influenced treatment intensification patterns.

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FIGURES AND TABLES

Figure 1. Flow diagram of patients diagnosed with de novo metastatic castration sensitive prostate cancer in Alberta, Canada and overall study inclusion. ADT: androgen deprivation therapy.

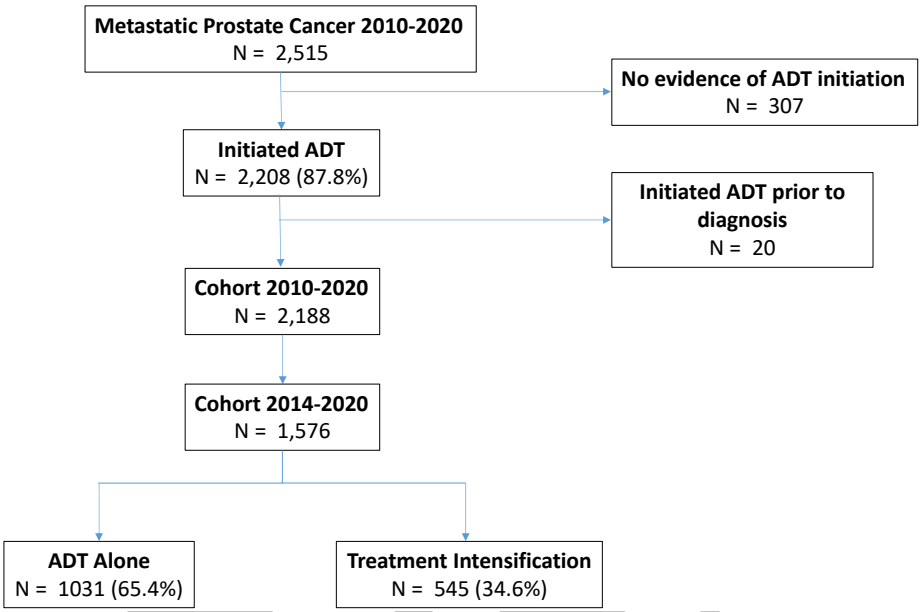
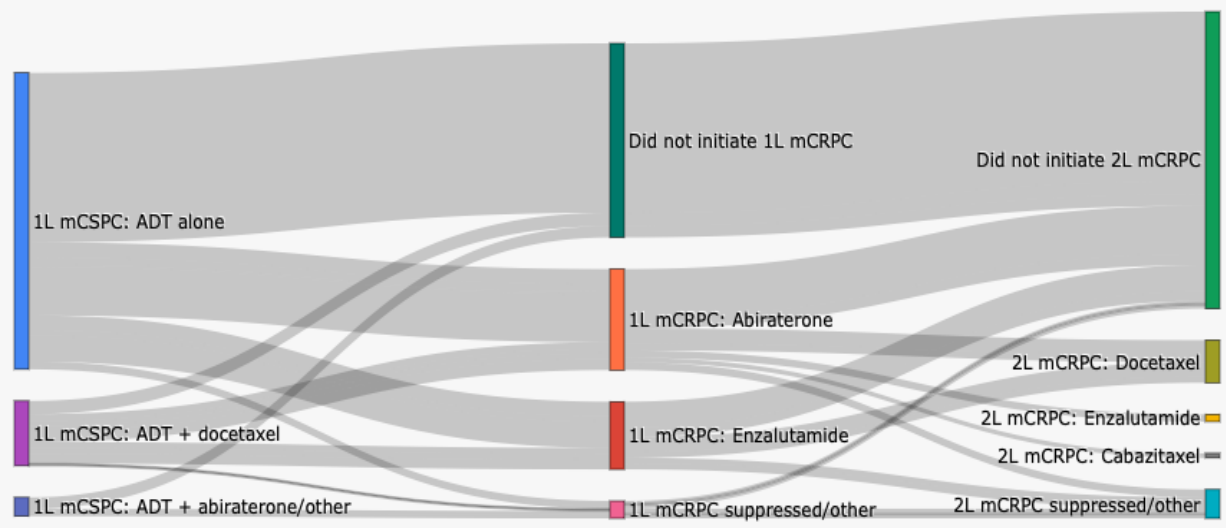


Figure 2. Treatment patterns of de novo metastatic castration sensitive prostate cancer in Alberta, Canada by treatment intensification era. (A) Sequencing of therapies from mCSPC to mCRPC in patients with mCSPC diagnosed between 2014 and 2017. (B) Sequencing of therapies from mCSPC to mCRPC in patients with mCSPC diagnosed between 2018 and 2020. ADT: androgen deprivation therapy; mCSPC: metastatic castration-sensitive prostate cancer; mCRPC: metastatic castration-resistant prostate cancer; 1L: first-line; 2L: second-line.

(A)



(B)

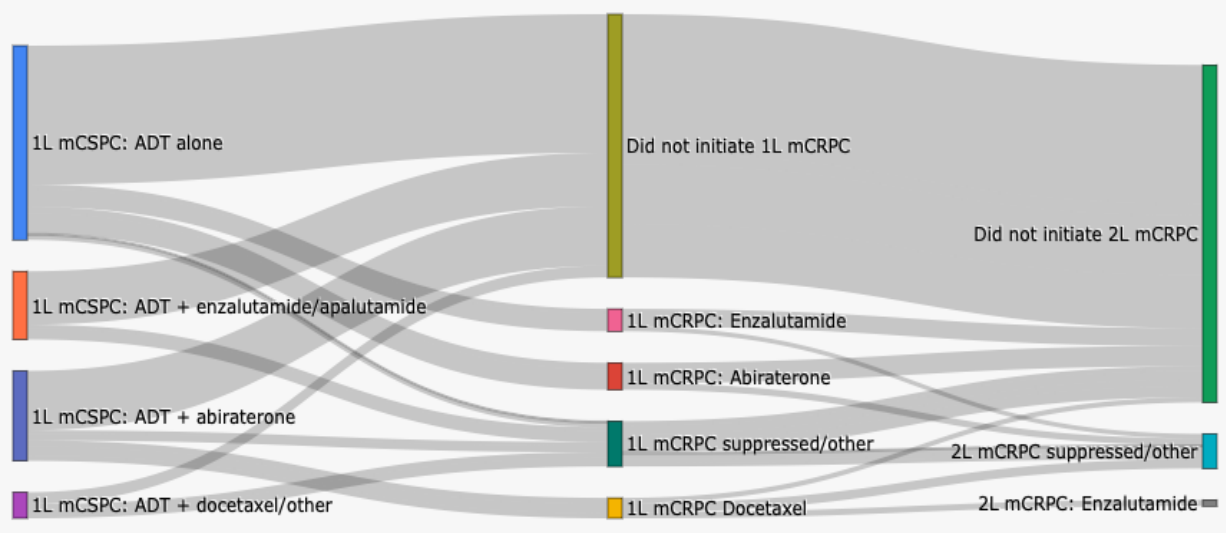


Figure 3. Cost-complexity pruned classification and regression tree to identify subgroups of patients who a have a high probability of treatment intensification among de novo metastatic castration sensitive prostate cancer in Alberta, Canada. The model identified age and year of diagnosis as the most important predictors of treatment intensification Probability of intensification is shown at the terminal node of the tree for each subgroup based on age and year at diagnosis combinations. mCSPC: metastatic castration sensitive prostate cancer.

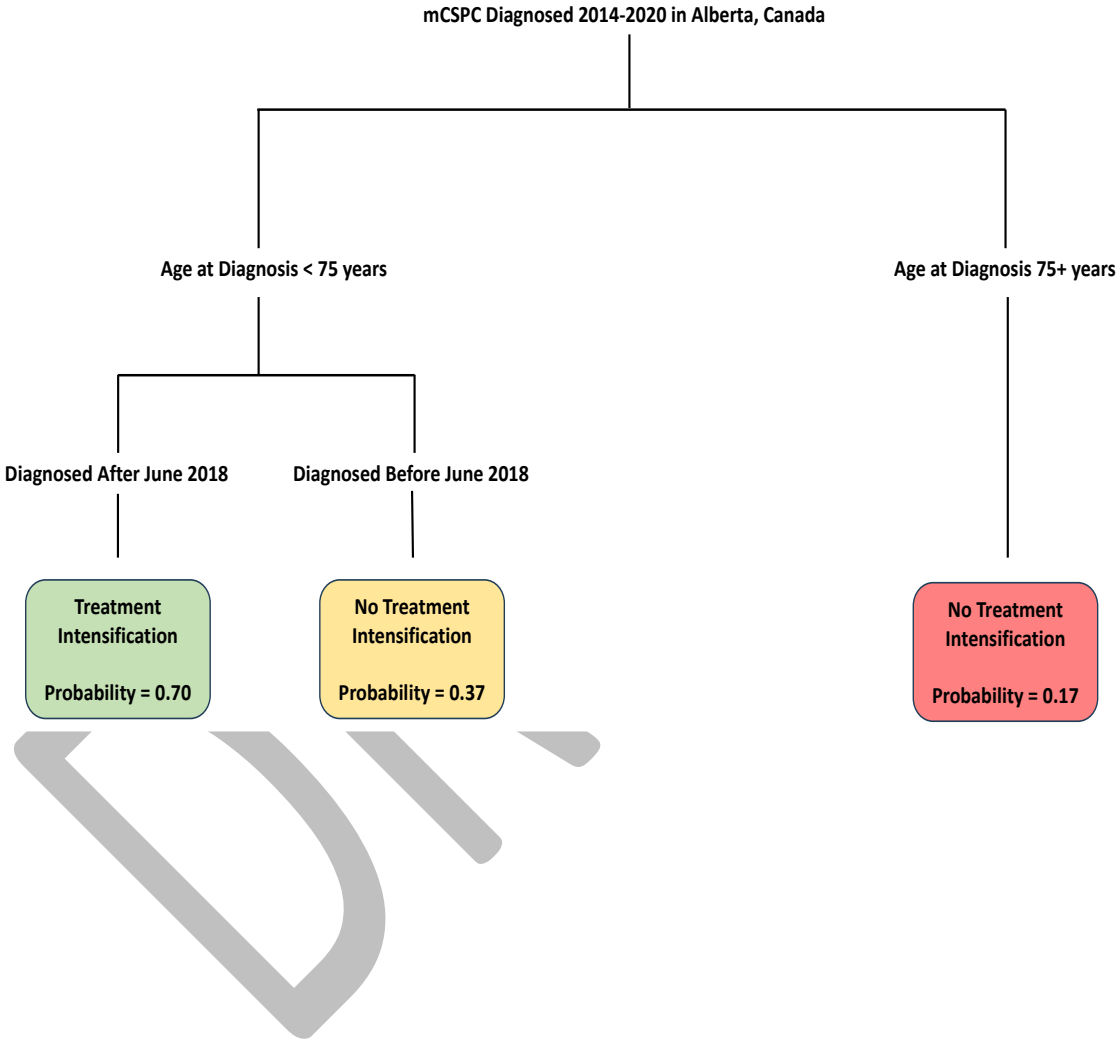


Table 1. Trends over time in specific treatments for de novo metastatic castration sensitive prostate cancer patients in Alberta, Canada from 2014 to 2020

Year	Total	ADT only	Docetaxel	Abiraterone	Apalutamide	Enzalutamide	Other
2014	186	150 (80.6)	30 (16.1)	<10	0 (0.0)	<10	<10
2015	185	144 (77.8)	33 (17.8)	<10	0 (0.0)	0 (0.0)	<10
2016	229	177 (77.3)	40 (17.5)	<10	0 (0.0)	<10	<10
2017	232	178 (76.7)	38 (16.6)	12 (5.2)	0 (0.0)	<10	<10
2018	246	146 (59.3)	22 (8.9)	76 (30.9)	0 (0.0)	0 (0.0)	<10
2019	240	137 (57.1)	<10	70 (29.2)	18 (7.5)	<10	<10
2020	258	99 (38.4)	10 (3.9)	31 (12.0)	98 (38.0)	15 (5.8)	<10

Cell counts less than 10 are suppressed in agreement with privacy regulations.
ADT: androgen deprivation therapy

Table 2. Predictors of treatment intensification with Apalutamide, Abiraterone, Enzalutamide, or chemotherapy among de novo metastatic castration sensitive prostate cancer patients in Alberta, Canada.

Variable	Overall (n=1576)	ADT alone (n=1031)	Treatment intensification (n=545)	Crude OR (95% CI)	Adjusted OR (95% CI)
Age, years					
<60	152 (9.6)	65 (6.3)	87 (16.0)	Ref	Ref
60–64	166 (10.5)	77 (7.5)	89 (16.3)	0.87 (0.55–1.36)	0.95 (0.54–1.64)
65–69	225 (14.3)	109 (10.6)	116 (21.3)	0.84 (0.55–1.28)	0.92 (0.55–1.53)
70–74	287 (18.2)	164 (15.9)	123 (22.6)	**0.55 (0.36–0.82)**	**0.58 (0.35–0.96)**
75–79	248 (15.7)	175 (17.0)	73 (13.4)	**0.31 (0.20–0.48)**	**0.42 (0.25–0.72)**

80+	498 (31.6)	441 (42.8)	57 (10.5)	**0.09 (0.06–0.15)**	**0.12 (0.07–0.21)**
Charlson comorbidity index (%**)**					
0	1036 (65.7)	632 (61.3)	404 (74.1)	Ref	Ref
1	241 (15.3)	169 (16.4)	72 (13.2)	**0.63 (0.46–0.86)**	0.73 (0.48–1.10)
2+	299 (19.0)	230 (22.3)	69 (12.7)	**0.46 (0.34–0.62)**	**0.64 (0.41–0.99)**
Number of metastases (%)					
1	1144 (72.6)	834 (80.9)	310 (56.9)	Ref	Ref
2	352 (22.3)	162 (15.7)	190 (34.9)	**3.06 (2.37–3.96)**	**2.19 (1.56–3.09)**
3+	80 (5.1)	35 (3.4)	45 (8.2)	**3.86 (2.41–6.23)**	**2.56 (1.40–4.74)**
Referral medical oncologist (%)					
No	596 (37.8)	542 (52.6)	54 (9.9)	Ref	Ref
Yes	980 (62.2)	489 (47.4)	491 (90.1)	**12.94 (9.17–18.77)**	**12.22 (8.07–19.07)**
Time to ADT					
<3 weeks	608 (38.6)	351 (34.0)	257 (47.2)	Ref	Ref
3–<6 weeks	374 (23.7)	248 (24.1)	126 (23.1)	**0.74 (0.56–0.97)**	0.73 (0.51–1.05)
6–<9 weeks	212 (13.5)	152 (14.7)	60 (11.0)	**0.57 (0.40–0.80)**	**0.52 (0.33–0.82)**
9+ weeks	382 (24.2)	280 (27.2)	102 (18.7)	**0.53 (0.39–0.70)**	**0.53 (0.40–0.71)**
Surgery (%)[1,2]					
No	1394 (88.5)	919 (89.1)	475 (87.2)	Ref	Ref
Yes	182 (11.5)	112 (10.9)	70 (12.8)	1.16 (0.83–1.60)	**2.18 (1.36–3.51**)

Radiation (%)[2]					
No	1503 (95.4)	993 (96.3)	510 (93.6)	Ref	Ref
Yes	73 (4.6)	38 (3.7)	35 (6.4)	**1.84 (1.15–2.96)**	**3.10 (1.52–6.36)**
Year					
2014	186 (11.8)	150 (14.5)	36 (6.6)	Ref	Ref
2015	185 (11.7)	144 (14.0)	41 (7.5)	1.16 (0.70–1.93)	0.92 (0.51–1.66)
2016	229 (14.5)	177 (17.2)	52 (9.5)	1.17 (0.73–1.91)	1.15 (0.66–2.02)
2017	232 (14.7)	178 (17.3)	54 (9.9)	1.21 (0.75–1.96)	1.17 (0.67–2.04)
2018	246 (15.6)	146 (14.2)	100 (18.3)	**2.83 (1.82–4.45)**	**3.10 (1.82–5.35)**
2019	240 (15.2)	137 (13.3)	103 (18.9)	**2.96 (1.91–4.70)**	**5.69 (3.27–10.06)**
2020	258 (16.4)	99 (9.6)	159 (29.2)	**8.40 (5.33–13.53)**	**14.23 (7.85–26.42)**

[1]Only includes transurethral resection of the prostate (TURP). [2]Prior to ADT
ADT: androgen deprivation therapy; CI: confidence interval; OR: odds ratio.

Table 3. Predictors of treatment intensification with apalutamide, abiraterone, enzalutamide, or chemotherapy among de novo metastatic castration-sensitive prostate cancer patients diagnosed in Alberta, Canada between 2014 and 2017

Variable	**Overall (n=832)**	**ADT alone (n=649)**	**Treatment intensification (n=183)**	**Crude OR (95% CI)**	**Adjusted OR (95% CI)**
Age, years					
<60	90 (10.8)	48 (7.4)	42 (23.0)	Ref	Ref
60–64	87 (10.5)	54 (8.3)	33 (18.0)	0.70 (0.58–1.32)	0.79 (0.40–1.52)
65–69	116 (13.9)	75 (11.6)	41 (22.4)	0.62 (0.36–1.10)	0.77 (0.41–1.43)

70–74	131 (15.7)	96 (14.8)	35 (19.1)	**0.42 (0.24–0.73)**	0.57 (0.30–1.05)
75–79	134 (16.1)	117 (18.0)	17 (9.3)	**0.17 (0.08–0.32)**	**0.24 (0.12–0.49)**
80+	274 (32.9)	259 (39.9)	15 (8.2)	**0.07 (0.03–0.13)**	**0.13 (0.06–0.26)**
Residence (%)[1]					
Rural	253 (30.4)	210 (32.4)	43 (23.5)	Ref	Ref
Urban	578 (69.6)	438 (67.6)	140 (76.5)	**1.56 (1.08–2.30)**	**1.72 (1.12–2.69)**
Charlson comorbidity index (%)					
0	550 (66.1)	408 (62.9)	142 (77.6)	Ref	Ref
1	124 (14.9)	102 (15.7)	22 (12.0)	**0.62 (0.37–1.00)**	0.63 (0.34–1.11)
2+	158 (19.0)	139 (21.4)	19 (10.4)	**0.39 (0.23–0.64)**	0.58 (0.31–1.04)
Number of metastases (%)					
1	639 (76.8)	526 (81.0)	113 (61.7)	Ref	Ref
2	155 (18.6)	99 (15.3)	56 (30.6)	**2.63 (1.79–3.87)**	**2.21 (1.40–3.50)**
3+	38 (4.6)	24 (3.7)	14 (7.7)	**2.72 (1.33–5.35)**	1.81 (0.79–4.08)
Referral medical oncologist (%)					
No	299 (35.9)	>289 (>44.5)	<10	Ref	Ref

Yes	533 (64.1)	356 (54.9)	>173 (>94.5))	**24.28 (11.56–62.40)**	**14.10 (6.55-36.80)**
Time to ADT					
< 3 weeks	294 (35.3)	212 (32.7)	82 (44.8)	Ref	Ref
3–<6 weeks	207 (24.9)	161 (24.8)	46 (25.1)	**0.74 (0.49–1.12)**	0.76 (0.46–1.23)
6–<9 weeks	122 (14.7)	100 (15.4)	22 (12.0)	**0.57 (0.33–0.95)**	**0.59 (0.31–1.06)**
9+ weeks	209 (25.1)	176 (27.1)	33 (18.0)	**0.49 (0.31–0.75)**	**0.55 (0.32–0.93)**
Surgery (%)[2,3]					
No				Ref	Ref
Yes	85 (10.2)	67 (10.3)	18 (9.8)	0.95 (0.53–1.61)	1.49 (0.75–2.88)
Year					
2014	186 (22.4)	150 (23.1)	36 (19.7)	Ref	Ref
2015	185 (22.2)	144 (22.2)	41 (22.4)	1.19 (0.72–1.97)	0.94 (0.52–1.68)
2016	229 (27.5)	177 (27.3)	52 (28.4)	1.22 (0.76–1.98)	1.12 (0.64–1.96)
2017	232 (27.9)	178 (27.4)	54 (29.5)	1.26 (0.79–2.04)	1.25 (0.72–2.19)

[1]One patient was missing postal code (1 for ADT). [2]Only includes transurethral resection of the prostate (TURP). [3]Prior to ADT. ADT: androgen deprivation therapy; CI: confidence interval; OR: odds ratio.

Table 4. Predictors of treatment intensification with apalutamide, abiraterone, enzalutamide, or chemotherapy among de novo metastatic castration-sensitive prostate cancer patients diagnosed in Alberta, Canada between 2018 and 2020

Variable	Overall (n=744)	ADT alone (n=382)	Treatment intensification (n=362)	Crude OR 95% CI)	Adjusted OR (95% CI)
Age, years					
<60	62 (8.3)	17 (4.5)	45 (12.4)	Ref	Ref
60–64	79 (10.6)	23 (6.0)	56 (15.5)	0.92 (0.43–1.92)	1.61 (0.64–4.09)
65–69	109 (14.7)	34 (8.9)	75 (20.7)	0.83 (0.41–1.65)	1.50 (0.65–3.40)
70–74	156 (21.0)	68 (17.8)	88 (24.3)	**0.49 (0.25–0.92)**	0.84 (0.38–1.78)
75–79	114 (15.3)	58 (15.2)	56 (15.5)	**0.37 (0.18–0.70)**	0.86 (0.38–1.92)
80+	224 (30.1)	182 (47.6)	42 (11.6)	**0.09 (0.04–0.16)**	**0.17 (0.08–0.37)**
Residence (%)[1]					
Rural	217 (30.0)	117 (31.1)	100 (28.8)	Ref	Ref
Urban	506 (70.0)	259 (68.9)	247 (71.2)	1.12 (0.81–1.54)	0.97 (0.62–1.50)
Charlson comorbidity index (%)					
0	486 (65.3)	224 (58.6)	262 (72.4)	Ref	Ref
1	117 (15.7)	67 (17.5)	50 (13.8)	**0.64 (0.42–0.96)**	0.86 (0.50–1.48)

2+	141 (19.0)	91 (23.8)	50 (13.8)	**0.47 (0.32–0.69)**	0.60 (0.34–1.04)
Number of metastases (%)					
1	505 (67.9)	308 (80.6)	197 (54.4)	Ref	Ref
2	197 (26.5)	63 (16.5)	134 (37.0)	**3.32 (2.36–4.74)**	**2.06 (1.30–3.30)**
3+	42 (5.6)	11 (2.9)	(8.6)	**4.41 (2.23–9.36)**	**2.96 (1.24–7.44)**
Referral medical oncologist (%)					
No	297 (39.9)	249 (65.2)	48 (13.3)	Ref	Ref
Yes	447 (60.1)	133 (34.8)	314 (86.7)	**12.25 (8.53–17.88)**	**13.45 (8.48–21.97)**
Time to ADT					
< 3 weeks	314 (42.2)	139 (36.4)	175 (48.3)	Ref	Ref
3-<6 weeks	167 (22.4)	87 (22.8)	80 (22.1)	0.73 (0.50–1.06)	0.67 (0.40–1.12)
6-<9 weeks	90 (12.1)	52 (13.6)	38 (10.5)	**0.58 (0.36–0.93)**	**0.48 (0.26–0.90)**
9+ weeks	173 (23.3)	104 (27.2)	69 (19.1)	**0.53 (0.36–0.77)**	**0.38 (0.22–0.65)**
Surgery (%)[2,3]					
No	647 (87.0)	337 (88.2)	310 (85.6)	Ref	Ref
Yes	97 (13.0)	45 (11.8)	52 (14.4)	1.26 (0.82–19.93)	**3.21 (1.71–6.12)**
Radiation (%)[3]					
No	703 (94.5)	370 (96.9)	333 (92.0)	Ref	Ref

Yes	41 (5.5)	12 (3.1)	29 (8.0)	**2.69 (1.38–5.55)**	**5.85 (2.15–17.63)**
Year					
2018	246 (33.1)	146 (38.2)	100 (27.6)	Ref	Ref
2019	240 (32.3)	137 (35.9)	103 (28.5)	1.09 (0.77–1.58)	**1.84 (1.14–3.00)**
2020	258 (34.7)	99 (25.9)	159 (43.9)	**2.35 (1.64–3.36)**	**4.80 (2.88–8.17)**

[1]21 patients were missing postal code (1 for ADT and 15 for treatment intensification). [2]Only includes transurethral resection of the prostate (TURP). [3]Prior to ADT. ADT: androgen deprivation therapy; CI: confidence interval; OR: odds ratio.