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Predictors of real-world utilisation of docetaxel combined with androgen deprivation therapy in metastatic hormone-sensitive prostate cancer

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Abstract

Background: Docetaxel has emerged as a standard-of-care for metastatic hormone-sensitive prostate cancer (mHSPC). Uptake of docetaxel for mHSPC in Australia has not previously been reported.

Aims: i) To investigate the real-world uptake of docetaxel in mHSPC; and ii) To identify predictors of utilisation of Docetaxel in mHSPC.

Methods: Men diagnosed from June 2014 to December 2018 and enrolled in the Prostate Cancer Outcomes Registry-Victoria (PCOR-Vic) were included. Data collected includes demographics, diagnosis method and institution, staging investigations, and treatments within 12 months of diagnosis. Wilcoxon rank-sum, chi-square and trend tests were used to identify predictors of docetaxel utilisation. All predictors were entered as covariates simultaneously into a multivariable logistic regression model. Statistical significance was set at 0.05 (two-sided).

Results: ~~Over the study period,~~ 1014 men with mHSPC were analysed, 25% of whom ~~men with mHSPC~~ received docetaxel with androgen deprivation therapy (ADT). Uptake of docetaxel increased from 20% in 2014 to 33% in 2018. Predictors of higher usage of docetaxel were younger age and treatment in a private hospital, with both remaining significant on multivariable analysis. Notably, the proportion of men under 70 receiving docetaxel increased from 54% in 2014-15 to 64% in 2016-18, while in men aged 70 and over the comparative figures were 15% and 22% respectively.

Conclusions: Although docetaxel was not used in a majority of cases, there was a clear increase in docetaxel uptake especially in younger men following publication of the CHAARTED and STAMPEDE trials. Identifying barriers to real-world implementation of pivotal clinical trial data is critical to improving outcomes in mHSPC.

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Introduction

Androgen deprivation therapy (ADT) by medical or surgical castration has been the mainstay of treatment for advanced prostate cancer since the pivotal discoveries of Huggins and Hodges in the 1940s(1). Although metastatic hormone-sensitive prostate cancer (mHPSC) responds initially to ADT in most cases, progression to metastatic castration-resistant prostate cancer (mCRPC) is inevitable and typically occurs within 12-18 months. This is an incurable condition with a median overall survival (OS) of under three years, thereby leading to efforts to intensify initial treatment of mHSPC and thereby deliver improved outcomes for men with advanced prostate cancer.

In May 2014, the CHAARTED trial (Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer; E3805; clinicaltrials.gov identifier NCT00309985)(2) was presented and demonstrated a significant improvement in OS for men treated with docetaxel + ADT over ADT alone. With a median follow-up of 53.7 months, the median OS was 57.6 months for docetaxel + ADT compared with 47.2 months for ADT alone (hazard ratio [HR], 0.72; 95% CI, 0.59 to 0.89; P = .0018). Benefit was restricted to patients with 'high-volume' disease (n = 513), with a median OS of 51.2 months for docetaxel + ADT versus 34.4 months with ADT alone (HR, 0.63; 95% CI, 0.50 to 0.79; P < .001). In comparison, in patients with 'low-volume' disease (n = 277), there was no improvement in OS with the addition of docetaxel to ADT (median OS 63.5 months vs. not reached; HR, 1.04; 95% CI, 0.70 to 1.55; P = .86)(3).

Two years later the STAMPEDE trial reported on outcomes in advanced prostate cancer patients treated with docetaxel combined with initiation of ADT(4). This multi-arm, multi-stage trial incorporated a mixed population of locally advanced and metastatic patients naïve to ADT. Median OS across the entire study was significantly longer in patients treated with docetaxel (81 months vs. 71 months; HR 0.78, 0.66–0.93; p=0.006). When only metastatic patients were

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considered, the magnitude of benefit from docetaxel appeared to be even greater (median OS 59 months vs. 43 months; HR = 0.81, 95% CI 0.69–0.95; P = 0.003). Importantly, in contrast to CHAARTED, there was no evidence of heterogeneity of docetaxel effect between low-volume and high-volume metastatic disease (interaction P = 0.827)(5).

CHAARTED and STAMPEDE established docetaxel as a standard-of-care option for mHSPC in patients fit to receive chemotherapy. Given the clinically meaningful benefit derived from docetaxel in these trials, it was anticipated that docetaxel would be widely adopted in the management of mHSPC patients. A survey of British uro-oncologists published in 2016 reported that 96% would prescribe docetaxel in this setting(6). However, real-world implementation of upfront docetaxel in mHSPC has been relatively low(7). In 2018, a consortium from Scotland reported 38% of mHSPC patients received docetaxel(8). Subsequently, in 2019 the England and Wales National Prostate Cancer Audit reported only 27% of mHSPC were treated with docetaxel(9). Most recently, a US-based survey of 156 physicians treating 1360 mHSPC patients found that only 4.1% patients received docetaxel with an additional 12% receiving a next-generation androgen receptor (AR) pathway inhibitor(10). In the latter study, presented at ASCO 2020, 64% of patients with mHSPC received ADT alone.

This pattern of docetaxel use seen overseas prompted us to look at Australian data on uptake of docetaxel in mHSPC following publication of the CHAARTED and STAMPEDE trials. We additionally investigated clinico-pathological factors correlated with use of docetaxel in mHSPC, in order to identify potential differences of application of the evidence between sub-groups of patients. These aims were examined using data from 1014 patients enrolled in a large, prospectively collected Australian prostate cancer registry.

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Methods

The Prostate Cancer Outcomes Registry-Victoria (PCOR-Vic) is a population-based prospective clinical quality registry of men with prostate cancer diagnosed in Victoria, Australia(11). Independent data collectors record clinicopathologic information regarding diagnosis, treatment and short-term follow up from hospital medical records and correspondences. This registry has been ethically approved (Ref no: HREC/16/Alfred/98). Participation is through an opt-out model.

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We included men diagnosed from June 2014 (following presentation of the CHAARTED data) to December 2018. We extracted clinical metastasis stage along with demographic factors such as age and residence, diagnosing method and institution, staging imaging, and all treatments within 12 months of diagnosis.

In regard to chemotherapy, an assumption was made that where chemotherapy was recorded by trained data collectors in the absence of a chemotherapy agent name being recorded, that docetaxel was used. The following conditions were imposed to provide further confidence that we were capturing docetaxel for mHSPC:

i. firstly, we excluded cases where a non-docetaxel chemotherapy regimen was specifically notated;
ii. secondly, we only included cases where docetaxel was commenced within 6 months of starting ADT. The cut-off of 6 months was chosen on the assumption that docetaxel started within 6 months of ADT would be for mHSPC, as opposed to mCRPC.
iii. Finally, we only included patients from June 2014 onwards, which coincides with the initial presentation of the CHAARTED data. This date was chosen on the basis that docetaxel administered prior to the release of CHARTED data would presumably have been for mCRPC.

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Specific ADT agent information was available for diagnoses in or after 2017. Geocoded residence was obtained from the Victorian Cancer Registry. Using Australian Bureau of Statistics correspondences, the residential address of each case was converted into remoteness areas (https://www.abs.gov.au/ausstats/abs@.nsf/mf/1270.0.55.005) and Socioeconomic Indexes for Areas (SEIFA) scores[*]), with the metric being the Index of Socioeconomic Advantage and Disadvantage. Remoteness was dichotomized into major metropolitan and regional/rural residence and SEIFA was split into quintiles.

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Statistical evaluation for predictors of receiving a docetaxel containing treatment versus ADT alone were performed with a Wilcoxon rank-sum test, chi-square test or Cuzick's test for trend. All of these predictors were then entered as covariates simultaneously into a multivariable logistic regression model with the Hosmer-Lemeshow test used to assess goodness-of-fit. Statistical significance was set at 0.05, tests were two-sided and all analyses and generation of figures were completed with Stata v14.0SE (College Station, TX).

Results

From June 2014 to December 2018 inclusive, 13157 men were diagnosed with prostate cancer and entered into the PCOR-Vic registry; of these, 1014 (7.7%) were coded as having clinically metastatic disease (cM1). The proportion of metastatic patients in the registry varied minimally year-to-year (range 6.9% - 8.8%). Compared to cM0 patients, cM1 patients were older (median: 74 vs 67 years), more likely to be from the most socioeconomically disadvantaged quintile (24% vs 16%) but not have a dissimilar area of residence (Major city residence 70% vs 71%).

Characteristics of the cM1 patients in this study are listed in Table 1. Diagnosis via TURP specimens or clinical imaging accounted for 35% of the patients. The proportion who had PET

[*] (https://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/2033.0.55.0012016

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imaging for primary staging was 14% overall, rising from 1.6% in 2014 to 34% in 2018. The most common M-category was M1b (65%) though no category was recorded in 23% of cases. In the years when ADT type was recorded, 2017 and 2018, the most common type was a Gonadotropin-releasing hormone(GnRH) analogue alone (78%), then a combination of GnRH analogue and first generation oral anti-androgen: bicalutamide, flutamide or nilutamide, (12%). Abiraterone or enzalutamide was a recorded treatment in 16 patients (4.0%).

Interventional treatment within 12 months of diagnosis (radiotherapy and/or prostatectomy) was received by 33% of patients, with no discernible trend over time noted (yearly range: 28% - 35%). Conversely, docetaxel containing treatment gradually increased over the study period, from 20% in 2014 to 25% in 2016 and then 33% in 2018 (Table 2 and Figure 1). Overall, 25% (254/1014) of cM1 patients received docetaxel. Younger men were more likely to be treated with docetaxel, with 45% (168/377) of patients aged under 70 receiving docetaxel compared with 14% (86/637) of patients age 70 and above.

Univariable comparisons between patients receiving ADT alone versus any docetaxel containing treatment, including with RT or RP, are presented in Table 3. Men who received docetaxel had a median age eleven years younger than those receiving ADT alone ($p<0.001$), with the majority (66%) aged under 70 years. A statistically significant difference was observed in type of diagnosing institution, with chemotherapy proportionally more common in patients diagnosed in a private hospital (39% vs 26%, $p<0.001$). No significant differences were observed between the groups in examining residence (major city or regional), ~~or~~ socioeconomic status or cM-category as predictors; though proportionally more patients receiving docetaxel vs ADT alone were stage M1c (7.9% vs 4.8%).~~.~~

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When analysed in a multivariable model, age remained a strong independent predictor while diagnosing institution was also an independent predictor (Table 4). There was no evidence of a lack of goodness-of fit. A five-year increase in age decreased the odds of receiving chemotherapy by 50% (OR=0.50, 95%CI: 0.445 – 0.56). Year of treatment also was an independent factor associated with use of docetaxel, the odds of adoption of chemotherapy steadily increasing during the study period. Compared to 2014, the odds of this modality were 1.831 times higher in 2016 and 2.5438 times in the years 2018. Of note, patient age appeared to influence the rate of uptake of docetaxel. For patients aged under 70 years (Figure 2), the percentage receiving docetaxel increased from 54% (45/83) to 64% (123/191) in the years 2014-15 and 2016-18 respectively. In comparison, adoption was proportionally lower for patients aged 70 and above with the corresponding percentages being 15% (22/143) and 22% (64/294).

Discussion

High-quality studies in the past five years have confirmed an overall survival benefit for men treated with combination approaches for mHSPC, rather than ADT alone. These combination approaches include not just docetaxel chemotherapy, but also androgen receptor pathway inhibitors (ARPIs) such as abiraterone acetate, enzalutamide and apalutamide(12). However, notwithstanding limitations in regulatory approvals and reimbursement for ARPIs for mHSPC, it is apparent that combination approaches with docetaxel are cost-effective(12, 13).

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Using the PCOR-Vic clinical quality registry we found that from June 2014 to December 2018, 25% of all men with mHSPC received docetaxel with ADT. Both younger age and treatment in a private hospital were associated with higher usage of docetaxel, with both remaining an independent predictor on multivariable analysis. Year of treatment was also a factor, with increasing adoption of docetaxel during the study period. Indeed, in 2018, 33% of patients received docetaxel compared to 20% in 2014. Taking into account both age and treatment year, it was

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notable that men under 70 had greater uptake of docetaxel versus ADT alone in comparison to men aged 70 and above.

Overall use of docetaxel in mHSPC (25%) in our registry was largely similar to prior reports of 38% from Scotland(8) and 27% from England and Wales(9). In comparison, a recent US series reported only 4.1% of mHSPC patients received docetaxel(10). While it might have been anticipated that easier access to new therapies in the US may have influenced these findings, only 12% of patients in the US series received a next-generation AR targeted agent. Therefore, just 16% of US patients received intensified upfront systemic therapy for mHSPC. Overall, these data point to broad under-utilisation of docetaxel in mHSPC, at least in Western countries. Moreover, in the Asia-Pacific region concerns about increased toxicity of docetaxel in Asian men may also contribute to low utilisation(7), as well as patient-reported concerns about level of knowledge of progression(14).

This study, and that from Scotland, were notable for attempting to identify clinico-pathological characteristics associated with docetaxel treatment in mHSPC. In the Scottish series, patients who did not receive were older (median 81 years vs. 68 years), had worse ECOG performance status (PS) (ECOG PS 2 29% vs. 3%) and lower haemoglobin (< 100 g/L 19% vs. 7%)(8). Although our registry did not collect ECOG PS or haemoglobin, we similarly found that patients who did not receive chemotherapy were older (median 78 years vs. 67 years). Altogether, these data point to lower adoption of upfront docetaxel in mHSPC patients considered to be less “chemo-fit”.

~~Nevertheless, ot~~Other factors also influence clinicians’ use of upfront docetaxel, including disease volume. The findings from CHAARTED and GETUG-15 study(15), comprising a predominantly low-volume mHSPC cohort, have understandably discouraged some clinicians from using docetaxel in patients with lower burdens of disease. On the other hand, data from STAMPEDE

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have shown benefit of upfront docetaxel in mHSPC irrespective of disease volume. Another point to consider was the increasing use of PSMA PET/CT during the study period, based on its superiority compared with conventional imaging(16). This may have led to an increase in use of docetaxel in lower burden disease through stage migration from low-volume (conventional imaging) to high-volume (PET imaging) metastatic disease. Similarly, PSMA PET/CT may have upstaged patients from M0 (on conventional imaging) to M1 disease (on PET). This could also have led to greater uptake of docetaxel.

Nevertheless, disease volume alone does not appear to account for the relatively low uptake of docetaxel in mHSPC. In England and Wales, where results from STAMPEDE have most strongly influenced treatment algorithms for mHSPC, 84% of surveyed centres in the National Prostate Cancer Audit believed low-volume metastatic disease was appropriate for docetaxel (the comparative figure for high-volume disease was 100%)(9). However, only 27% of all patients received docetaxel in this audit, indicating somewhat of a disconnect between interpretation of high-level evidence and implementation into real-world practice.

We postulate several reasons for why this may be the case. Undoubtedly, patient factors such as age and co-morbidities impact on perceived "chemo-fitness", with age being an independent predictor in this study. This is a particularly pertinent consideration given the age profile of patients with newly diagnosed prostate cancer. This underscores the importance of formal geriatric assessment in metastatic prostate cancer patients. In a recent randomised study of > 70 year old patients with cancer commencing systemic therapy, comprehensive geriatric assessment and management led to significant improvements in functional and quality of life scores, lower unplanned admissions and lower rates of early treatment cessation(17). Therefore, early referral of mHSPC patients to a geriatric oncology clinic is paramount to optimising use of systemic therapy.

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Other factors also influence real-world use of docetaxel in mHSPC patients. For example,~~Similarly,~~ treating institution ~~may~~ appears to be a factor, with treatment in a private hospital being another independent predictor for use of docetaxel in this study. Presentation after prior local therapy may additionally influence treatment choices, with the relatively long survival for low-volume relapsed metastatic disease (median OS > 7.5 years)(18) potentially swaying some clinicians against employing upfront docetaxel. ~~Finally~~Additionally, the role of urologists as traditional gate-keepers of this population must be considered. For many decades urologists have managed mHSPC patients from diagnosis and initiation of ADT, through to the development of mCRPC. It is possible that this could lead to lower use of docetaxel in many countries, since relatively few urologists routinely prescribe chemotherapy and they are becoming more comfortable with the use of AR pathway inhibitors in mHSPC(19). However, oncology multidisciplinary team (MDT) meetings are now widely prevalent in the public and private hospital systems in Australia, providing a valuable channel for facilitating cross referrals to other specialties. Notably, a previous Australian study found that cross-disciplinary referrals at MDT meetings occurred in 26% of prostate patients(20). It is plausible that such referrals and consequent early engagement of medical oncology result in greater use of docetaxel in mHSPC.

A key limitation of our analysis is the difficulty in assessing what benchmark should be set for docetaxel use in the PCOR-Vic registry. In part, this is due to the absence of disease characteristics such as metastatic volume (high versus low). As such, it is not possible to ascertain the proportion of patients with high volume metastatic disease, for whom the evidence supporting use of docetaxel is strongest. Likewise, some psycho-social factors potentially influencing variations in care are not fully captured in PCOR-Vic. These include accessibility of specialist medical care (e.g., urologists, medical oncologists and geriatricians), degree of family and social supports, employment status, and medical comorbidities. All of these could impact on use of docetaxel in

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the mHSPC setting, as could the availability of comprehensive geriatric assessment and MDT meetings as discussed above.

In addition, the PCOR-Vic registry does not collect patient preference, which is a critical consideration in the use of cytotoxic therapy. For example, in a recent mixed-methods study of men with metastatic prostate cancer(21), 72% strongly agreed with "wanting to feel well enough to spend quality time with loved ones", narrowly higher than 65% for whom "optimising treatment efficacy" was strongly endorsed. This speaks to the desire of a majority of men with metastatic prostate cancer to avoid substantial toxicity impacting quality-of-life, even at the expense of maximising therapeutic outcomes.

We acknowledge ~~multiple~~ other limitations of our study and data available from the PCOR-Vic registry. Coverage of all prostate cancer diagnoses in the state is not total within PCOR, increasing from 60% to 85% over 2014-2018. Furthermore, we were not able to report on ~~metastatic disease volume nor on~~ long-term outcomes of treatment. Lastly, the registry captures newly diagnosed patients and therefore for the purposes of this study was biased towards de novo as opposed to relapsed metastatic patients.

Conclusion

In conclusion, from June 2014 to December 2018, one-quarter of men enrolled in the PCOR-Vic registry received upfront docetaxel for mHSPC. During the period of the study, there was a gradual increase in the uptake of docetaxel, with one-third of men receiving docetaxel in 2018. Our data are generally consistent with prior reports and point to the need for a multi-faceted approach to optimise upfront systemic therapy for mHSPC. Notably, advanced age was a key barrier to use of docetaxel, which highlights the importance of careful assessment of chemo-fitness in older patients. The increasingly recognised role of formal geriatric oncology programs (17) may be

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useful in this respect. Understanding barriers to the use of docetaxel in public hospitals is also paramount and worthy of further investigation. Focused educational programs for clinicians that seek to improve the implementation of practice-changing clinical trial data will likewise be critical to enhancing outcomes for men with mHSPC. Future research endeavours should prioritise capture of longer-term data from mHSPC patients including utilisation of subsequent systemic agents to characterise treatment sequencing in a real-world setting. In addition, it will be vital to report on the uptake of each of the life-prolonging treatment modalities available in the mHSPC setting including docetaxel, ARPIs and high-dose palliative radiotherapy to the prostate, as well as the factors influencing utilisation of each.

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Figure Legends

Figure 1: Treatments received within 12 months of diagnosis per year of diagnosis
Figure 2: Stacked 100% bar chart of ADT alone vs any docetaxel containing treatment per year split by age at diagnosis

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Table 1: Characteristics of cM1 men included in this study (n=1014).
TURP = transurethral resection of prostate, ADT = androgen deprivation therapy, RT = radiation therapy

	N (%) unless stated
Age at diagnosis, median (IQR)	74 (66 – 81)
Residence	
Major metropolitan	671 (66)
Regional/rural	287 (28)
Not recorded	56 (5.5)
Socioeconomic status	
1st Quintile (most disadvantaged)	226 (22)
2nd Quintile	201 (20)
3rd Quintile	165 (16)
4th Quintile	156 (15)
5th Quintile (most advantaged)	207 (20)
Not recorded	59 (5.8)
Year of diagnosis	
2014*	124 (12)
2015	208 (21)
2016	226 (22)
2017	230 (23)
2018	226 (22)
Diagnosis method	
Prostate biopsy	543 (54)
TURP	141 (14)
Imaging	215 (21)
Metastasis biopsy	78 (7.7)
Other/Unknown	37 (3.6)
Diagnosing institution	
Public	641 (63)
Private	358 (35)
Not recorded	15 (1.5)
Staging imaging modality	
PET	146 (14)
Conventional imaging **	812 (80)
Not recorded	56 (5.5)
M-category	
M1a	62 (6.1)
M1b	661 (65)
M1c	61 (6.0)
M1 – not otherwise categorised	230 (23)
Treatment in first 12 months	
ADT	457 (45)
ADT + Chemo	176 (17)
ADT + RT/Surgery	195 (19)
ADT + Chemo + RT/Surgery	78 (7.7)

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RT/Surgery	57 (5.6)
Observation/Not recorded	51 (5.0)

** Only from June 2014*

*** Conventional Imaging = CT and/or Bone Scan*

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Table 2: Treatments received within 12 months of diagnosis per year of diagnosis, n (column %)
*ADT = androgen deprivation therapy. Intervention = radical prostatectomy or radiation therapy. * Only from June 2014*

	Year				
Treatment	2014*	2015	2016	2017	2018
ADT	60 (48)	99 (48)	96 (42)	100 (43)	102 (45)
ADT+Docetaxel	18 (15)	28 (13)	45 (20)	37 (16)	48 (21)
ADT+Intervention	18 (15)	38 (18)	48 (21)	52 (23)	39 (17)
ADT+ Docetaxel +Intervention	7 (5.6)	14 (6.7)	12 (5.3)	19 (8.3)	26 (12)
Intervention	10 (8.1)	17 (8.2)	16 (7.1)	9 (3.9)	5 (2.2)
Unknown/Observation	11 (8.9)	12 (5.8)	9 (4.0)	13 (5.7)	6 (2.7)
Any docetaxel	*25 (20)*	*42 (20)*	*57 (25)*	*56 (24)*	*74 (33)*

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Table 3: Comparison of patients receiving ADT alone vs any docetaxel containing regime. Percentages are within treatment type (columns) unless stated. p-values do not include "not recorded" category.

	ADT only n=457 N (%)	Docetaxel containing n=254 N (%)	p-value
Age at diagnosis, median (IQR)	78 (71 – 84)	67 (60 – 72)	<0.001
Age group			
<70 years	106 (23)	168 (66)	<0.001
≥70 years	351 (77)	86 (34)	
Residence			
Major metropolitan	302 (66)	177 (70)	0.71
Regional/rural	124 (27)	68 (27)	
Not recorded	31 (6.8)	9 (3.5)	
Socioeconomic status			
1st Quintile (most disadvantaged)	105 (23)	50 (20)	0.79
2nd Quintile	91 (20)	52 (20)	
3rd Quintile	73 (16)	43 (17)	Trend=0.32
4th Quintile	62 (14)	41 (16)	
5th Quintile (most advantaged)	94 (21)	55 (22)	
Not recorded	32 (7.0)	13 (5.1)	
Year of diagnosis			
2014 *	60 (13)	25 (9.8)	0.14
2015	99 (22)	42 (17)	
2016	96 (21)	57 (22)	Trend=0.012
2017	100 (22)	56 (22)	
2018	102 (22)	74 (29)	
Diagnosing institution			
Public	329 (72)	150 (59)	<0.001
Private	120 (26)	99 (39)	
Not recorded	8 (1.8)	5 (2.0)	
M-category			
M1a	26 (5.7)	12 (4.7)	0.17
M1b	316 (69)	160 (63)	
M1c	22 (4.8)	20 (7.9)	
M1 – not otherwise categorised	93 (20)	62 (24)	

** Only from June 2014*

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Table 4: Multivariable logistic regression for odds of docetaxel containing therapy versus ADT alone therapy. The most common M-category (M1b) is set as the reference for that variable. Patients without recorded data for all covariates excluded from the model (n=656).

	Odds ratio (95% CI)
Age, per 5 year increase	0.50 (0.44 – 0.56)
Residence	
Major metropolitan	1.0
Regional/rural	1.00 (0.63 – 1.56)
Socioeconomic status	
1st Quintile (most disadvantaged)	1.0
2nd Quintile	1.10 (0.62 – 1.95)
3rd Quintile	1.14 (0.61 – 2.12)
4th Quintile	1.23 (0.64 – 2.35)
5th Quintile (most advantaged)	1.01 (0.55 – 1.86)
Year of diagnosis	
2014	1.0
2015	1.17 (0.55 – 2.49)
2016	1.83 (0.88 – 3.84)
2017	1.72 (0.83 – 3.58)
2018	2.53 (1.23 – 5.22)
Diagnosing institution	
Public	1.0
Private	2.22 (1.44 – 3.42)
M-category	
M1a	0.45 (0.18 – 1.11)
M1b	1.0
M1c	1.44 (0.62 – 3.31)
M1 – not otherwise categorised	1.10 (0.69 – 1.76)

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Declaration of Interests

Dr. Azad reports personal fees, non-financial support and other from Janssen , grants, personal fees, non-financial support and other from Astellas, grants, personal fees, non-financial support and other from Novartis, grants, personal fees, non-financial support and other from Merck Serono, personal fees, non-financial support and other from Tolmar, personal fees, non-financial support and other from Amgen, grants, personal fees, non-financial support and other from Pfizer, personal fees and other from Bayer, personal fees and other from Telix Pharmaceuticals, grants, personal fees and other from Bristol-Myers Squibb, grants, personal fees and other from Sanofi, personal fees and other from Noxopharm, grants, personal fees and other from Astra Zeneca, grants from Glaxo Smith Kline, grants from Aptevo Therapeutics, grants from MedImmune, grants from Bionomics, grants from SYNthorx, personal fees and other from Ipsen, personal fees and other from Merck Sharpe Dome , outside the submitted work; .

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