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Adoption of Intermittent Androgen Deprivation Therapy for Advanced Prostate Cancer: A Population Based Study in American Urology Practice

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Abstract

Introduction—In several developed countries intermittent androgen deprivation therapy has been accepted over continuous androgen deprivation therapy for advanced prostate cancer management. To our knowledge its adoption and predictors of use in American urology practice remain unknown.

Methods—Using SEER-Medicare data we identified a cohort of men 66 years old or older who were newly diagnosed with prostate cancer with metastasis or with treated recurrence in whom androgen deprivation therapy was started during 2003 to 2007. We determined intermittent androgen deprivation therapy receipt based on interruptions longer than 3 months between scheduled and actual therapy injections, and physician visits and prostate specific antigen tests during the interruption. Predictors included patient and physician characteristics. We performed logistic regression analysis separately in the metastatic and treated recurrence groups using generalized estimating equations to account for the clustering effect of patients treated by the same physician.

Results—Our cohort included 4,281 men, of whom 2,487 with metastasis and 1,794 with treated recurrence received intermittent androgen deprivation therapy. In patients who received intermittent rather than continuous therapy the median duration of therapy was by 6.4 and 9.0 months longer in those with metastasis and treated recurrence, respectively. Each patient group showed significant variation in intermittent therapy use by region ($p < 0.0001$). There was lower intermittent androgen deprivation therapy use in the Eastern and Central regions than in the Mountain and Pacific regions.

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Conclusions—Intermittent androgen deprivation therapy has not been widely used in American urology practice. Its adoption shows substantial variation by geographic regions. These regional differences likely reflect uncertainty regarding the efficacy of this therapy among providers as well as differences in patient preferences and involvement in treatment decision making.

Keywords

prostatic neoplasms; gonadotropin-releasing hormone; physician's practice patterns; neoplasm recurrence; local; neoplasm metastasis

Androgen deprivation therapy has been the primary palliative treatment for metastatic PCa since the 1940s.¹ It is increasingly given as salvage therapy for recurrent PCa following remission.² ADT is administered in approximately 600,000 patients with PCa in the U.S. annually to delay disease progression.³

More than 95% of ADT in the U.S. is administered by injections of GnRH agonists⁴ but its optimal administration remains uncertain. Convention in the U.S. is to give patients CADT involving periodic ADT until the disease stops responding. Medical ADT can also be administered intermittently by alternating between periods on and off cycle with treatment durations based on PSA values. Variations of IADT exist but typically ADT is suspended when PSA in patient decreases to 4 ng/ml. It is re-initiated when PSA approaches a prespecified threshold (eg 10 ng/ml in recurrent cases or 20 ng/ml in metastatic cases). A meta-analysis of 8 randomized clinical trials concluded that patients receiving IADT had similar overall and progression survival but were less likely to have hot flushes, gynecomastia and headaches than men receiving CADT.⁵ Although IADT has been endorsed as first line hormonal therapy for advanced PCa by the EAU (European Association of Urology)⁶ and the UK National Institute for Health and Clinical Excellence⁷ for improved quality of life during off treatment periods⁸ and reduced cost, the U.S. has no guidelines explicitly endorsing IADT.

Given the potential impact of widespread IADT adoption on the increasing number of PCa survivors (due to the aging U.S. population), tracking IADT uptake is important. To our knowledge no previous study has examined IADT patterns and predictors in American urology practice. Implementation of the MMA (Medicare Modernization Act) in 2004 decreased the profit incentive associated with ADT prescriptions by more than 50%,⁹ affecting patterns of ADT administration in PCa care,^{10,11} which may have influenced IADT adoption. We further investigated the use of IADT vs CADT and its related factors in a population based sample.

Materials and Methods

Data Source

We performed a retrospective cohort study using the linked SEER-Medicare data set.¹² The SEER program is a population based cancer registry that collects cancer incidence data in approximately 26% of the population of the U.S. Collected data include sociodemographics, diagnosis year, clinical stage, Gleason sum, PSA level and cancer directed treatment within 6 months after diagnosis. The NCI performs regular linkages between SEER and Medicare

claims data,¹³ and makes these data available to investigators. We used 3 types of Medicare claims to assess comorbidities and ADT use, including inpatient hospital records, physician claims and outpatient bills from institutional providers. We also obtained linked data on physician demographics, medical specialty and years of practice through NCI using Medicare encrypted UPINs (Unique Physician Identifier Numbers) matched with data from the AMA (American Medical Association) Physician Masterfile.

Patient Population

Our study population included 8,616 men 66 years old or older with advanced PCa diagnosed during 2002 to 2007 who started ADT between 2003 and 2007, and were followed until 2010. The minimum age of 66 years allowed us to ascertain chronic comorbidities at least 1 year after entering Medicare at age 65 years. Restricting the patient population to men who started ADT no later than 2007 was based on our data showing that it took an average of 3 years of followup to observe ADT re-initiation for IADT. Advanced PCa included newly diagnosed metastatic disease and recurrent disease with salvage ADT, defined as ADT initiated at least 6 months after prostatectomy or the final course of radiation therapy. Men were excluded from study if they 1) were without continuous Medicare coverage or enrolled in health maintenance organizations (1,668), 2) underwent orchiectomy (159), 3) had errors in Medicare claims (297), such as claims after death (14), receiving ADT more than 3 months before PCa diagnosis (82), duplicate ADT records on the same day (103) or unmatched drug code and unit information for ADT codes (98), or 4) died within a year after ADT initiation (1,317) because of insufficient followup time to verify IADT receipt, which included a 6 to 8-month induction period, or 5) received only 1 ADT injection (436) of which the pattern of administration could not be classified as CADT or IADT (8) and had an induction period shorter than 3 months (290). Our final study cohort included 2,487 patients with metastatic disease and 1,794 with treated recurrence.

Treatment Characteristics

We used HCPCS (Health Common Procedure Coding System) codes J9202, J1950, J9217, J9219, J9218, J9225 and J3315 to identify dates and doses of GnRH agonists use with and without antiandrogens. ADT initiation date was the first ADT date for patients with metastatic PCa, or the first ADT date postoperatively or radiation for patients with recurrent PCa. We used unit designation information on each ADT cycle to determine the duration of the current ADT injection and project the scheduled date of the next ADT cycle.¹⁴ Patients with claims indicating periodic receipt of GnRH agonists with delays less than 3 months from scheduled dates of ADT were designated as receiving CADT. For IADT men needed to meet 3 criteria. The first 2 criteria were that men 1) received ADT in at least 2 separate treatment cycles with at least a 3-month gap between scheduled and actual dates of the next ADT and 2) the first ADT off cycle started within 18 months after ADT initiation to capture the intent to administer IADT. To avoid inadvertently including nonadherent patients as those receiving treatment off cycle we explored 5 ADT cycle gap requirements. In order of increasing restrictions for criterion 3 the requirements included 3a) 1 physician visit, 3b) 1 PSA test, 3c) 1 physician visit and 1 PSA test, 3d) 2 PSA tests, and 3e) 1 physician visit and 2 PSA tests. We compared results across these different definitions. Tables 1 and 2 list

results with the IADT definition by criteria 1, 2 and 3a. Results by criteria 1, 2 and 3e are available upon request.

Covariate Measurement

We included patient and physician characteristics as potential correlates for IADT receipt, including year of ADT initiation, age at ADT initiation, race/ethnicity, marital status at diagnosis, quartiles of high school graduation percent at the census tract level, geographic region, Charlson comorbidity index, history of hypertension, diabetes, myocardial infarction, stroke, hyperlipidemia and fracture using inpatient plus outpatient claims within 1 year before ADT initiation, cancer sequence, physician training in the U.S. and physician years of practice. The treating physician was defined as the physician whom the patient visited most frequently for ADT.

Statistical Analysis

We performed all analyses of metastatic and recurrent subgroups separately due to their clinical distinctions and different risk-benefit profiles of IADT use. We first compared patient characteristics by disease group. We then calculated the predicted probability of IADT receipt by geographic region and year of diagnosis from the final logistic regression model.^{15,16} We then assessed differences in patients with IADT and CADT across a range of socio-demographic, clinical and physician characteristics using the chi-square test. Finally we performed multiple logistic regression models with IADT receipt as the dependent variable, and patient and physician characteristics as independent variables to estimate adjusted associations, measured as the OR, between each variable and IADT use. We applied generalized estimating equations with an exchangeable working correlation structure in final regression models to account for clustering effects resulting from groups of patients treated by the same physician. All analysis was done with SAS®, version 9.2.

Handling of Missing Data

A total of 160 patients lacked physician characteristic information. We performed multiple imputations by including all previously mentioned covariates and ADT type in the imputation models to generate 5 multiple imputed data sets with estimates filled in for missing values. Results from the separate analyses of these data sets were pooled using the Rubin rule.¹⁷ We performed sensitivity analysis using the imputed data sets and compared the results with those of the complete case data.

Results

Study Population

We identified 2,487 patients with metastatic disease and 1,794 with treated recurrence. Median age was 76 years. Most patients were white (84%) and married (67%), and PCa was the first or only cancer (88%). The metastatic group tended to be younger at ADT initiation, reside in the Eastern geographic region and have less comorbidity (table 1). Median followup was 38.4 and 48.0 months in the metastatic and recurrent groups, respectively. The mortality rate was 67% (median survival 27.6 months in 1,661 patients) and 37% (median

survival 32.4 months in 670) during followup in the metastatic and recurrent groups, respectively.

IADT Use Patterns

IADT was administered in 21% and 28% of metastatic and recurrent cases, respectively. In metastatic cases ADT initiation after diagnosis was later in the IADT group than in the CADT group (median 3.7 vs 2.9 months). In the 2,331 men who died during the study the median ADT duration in the IADT and CADT groups was 25.8 and 19.4 months in patients with metastasis, and 27.7 vs 18.7 months, respectively, in those with recurrence.

The predicted probability of IADT was 18% in the Eastern and Central regions, and 25% in the Mountain, Western and Pacific regions in the metastatic group. In the recurrent group the predicted probability was 23% in the Eastern and Central regions, and 33% in the remaining areas. Overall IADT was administered less in patients with PCa who had metastasis than in those with treated recurrence.

Patient and Physician Characteristics Associated with IADT

IADT adoption increased from 2003 to 2006 in the metastatic and recurrent groups with a slight increase in 2007 in the metastatic group (OR 1.43, table 2). Our data also indicated similar patterns of significant geographic variations in IADT after adjusting for all other factors in each group. In the recurrent group only we noted lower IADT use in men with a history of hypertension (OR 0.75, 95% CI 0.58–0.96, table 3).

On our sensitivity analyses using imputed data sets (data available upon request) we obtained the same general results as with our model using only complete cases (tables 2 and 3). We also reached similar conclusions on analyses in which IADT was defined more conservatively, requiring at least 2 PSA tests and 1 physician visit during the suspended period (data available on request).

Discussion

IADT has been the recommended strategy for advanced PCa in the UK, European Union and Canada. While there has been some IADT use in the U.S., it is still far less commonly administered. To our knowledge this is the first population based study documenting the prevalence of IADT in American practice and the substantial geographic variation in IADT use, adjusting for several patient and physician characteristics.

The substantial variation in IADT by region likely reflects variability in urologist perceptions of the risk-benefit trade-offs of IADT vs CADT in men who experience metastasis or treated recurrence. A comprehensive review of the literature suggests that physician attitudes and beliefs are the most important factors explaining regional variation in treatment.¹⁸ Currently there is no formal consensus on IADT use in guidelines in the U.S. and mixed evidence on the efficacy of IADT vs CADT may affect the propensity of different urologists to prescribe IADT as an alternative to CADT. Geographic variation in IADT may also reflect regional differences in patient preferences of intensive disease control and favorable quality of life, and their involvement in shared treatment decision

making.¹⁸ Future research into physician beliefs and patient awareness regarding IADT may improve our understanding of factors contributing to geographic variation.

Two recent trials of the comparative efficacy of IADT and CADT are expected to help consolidate clinical consensus on IADT and influence IADT uptake. In a study of 1,386 men with a median followup of 6.9 years Crook et al concluded that IADT did not compromise patient survival but rather improved quality of life, favoring IADT for patients experiencing rising PSA after radio-therapy.¹⁹ Another study of 1,535 men with metastatic PCa with a median of 9.2 years of followup showed that IADT may potentially lead to a higher risk of death than CADT (HR 1.1, 95% CI 0.99–1.23) based on a noninferiority clinical trial design showing only a small improvement in quality of life.²⁰ Future studies will shed light on the influence of data from these large trials of IADT adoption.

Our data do not support our hypothesis that men with a history of ADT associated comorbidities such as diabetes, hypertension and stroke would be more likely to receive IADT. In 2010 concerns regarding risks associated with ADT led the FDA (Food and Drug Administration) to revise safety labels advising health care providers to periodically monitor ADT users for signs of diabetes and cardiovascular disease.²¹ Although reduced cycles of ADT injections as in IADT have not been proven to decrease ADT associated adverse events,⁵ ADT associated adverse events have been reported to be dose dependent.¹⁴ More evidence on the long-term risks of IADT vs CADT could help inform shared decision making on IADT use.

Several limitations should be noted. Although the SEER program is the most representative population based cancer registry in the U.S., data are not collected on the entire American population. Because we could not use PSA levels to define IADT due to lack of longitudinal PSA data, we explored different IADT definition criteria to ensure the robustness of our reliance on Medicare claims to track ADT delivery. We also could not separate metastatic cases with only positive nodes and symptomatic bone metastasis due to the lack of imaging results.

Conclusions

Briefly, IADT has been adopted at moderate levels (between 21% and 28%) for patients with PCa who have metastasis or treated recurrence in the U.S. However, substantial geographic variation exists in IADT adoption, underscoring uncertainty and disagreement about the relative value of IADT vs the more established CADT. It is not yet clear whether recent data will reveal greater IADT use with less geographic variation. More research comparing the long-term effectiveness and safety profiles of IADT and CADT in usual practice may further inform shared clinical decision making.

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Abbreviations and Acronyms

ADT	androgen deprivation therapy
CADT	continuous androgen deprivation therapy
GnRH	gonadotropin-releasing hormone
IADT	intermittent androgen deprivation therapy
NCI	National Cancer Institute
PCa	prostate cancer
PSA	prostate specific antigen
SEER	Surveillance, Epidemiology and End Results
UK	United Kingdom
U.S.	United States

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Table 1

Description of sociodemographic and clinical characteristics among 4,281 men 66 years and older with advanced prostate cancer (newly diagnosed metastasis or treated recurrence) who started androgen deprivation therapy during 2003 – 2007 and were followed until December 31, 2010.

	Total	Metastatic	Recurrent	p-value
Population Characteristics	N (column %)	N (column %)	N (column %)	
Status of disease				
Metastatic	2,487 (58%)			
Recurrent	1,794 (42%)			
I. Sociodemographic Factors				
Year of ADT initiation				
2003	648 (15%)	521 (21%)	127 (7%)	<0.0001
2004	797 (19%)	517 (21%)	280 (16%)	
2005	770 (18%)	473 (19%)	297 (17%)	
2006	107 (24%)	497 (20%)	540 (30%)	
2007	1,029 (24%)	479 (19%)	550 (31%)	
Age at initiation of ADT				
66–70	577 (13%)	463 (19%)	114 (6%)	<0.0001
71–75	1011 (24%)	589 (24%)	422 (24%)	
76–80	1046 (24%)	575 (23%)	471 (26%)	
80+	1647 (38%)	860 (35%)	787 (44%)	
Race/Ethnicity				
White	3,592 (84%)	2,081 (84%)	1,511 (84%)	0.60
African-American	419 (10%)	243 (10%)	176 (10%)	
Asian	100 (2%)	56 (2%)	44 (2%)	
Other	170 (4%)	107 (4%)	63 (4%)	
Married				
No	1,425 (33%)	810 (33%)	615 (34%)	0.24
Yes	2,856 (67%)	1,677 (67%)	1,179 (66%)	
Group (Census Tract) Level of High School Graduate Percentage in Quartiles ^a				0.09
Q1	1,189 (28%)	716 (29%)	473 (26%)	
Q2	1,064 (25%)	630 (25%)	434 (24%)	
Q3	1,008 (24%)	555 (22%)	453 (25%)	
Q4	932 (22%)	541 (22%)	391 (22%)	
Registry Site				<0.0001
West/Pacific	1,732 (40%)	1,088 (44%)	644 (36%)	
Eastern	1,013 (24%)	568 (23%)	445 (25%)	
Central	1,080 (25%)	609 (24%)	471 (26%)	
Mountain	196 (5%)	97 (4%)	99 (6%)	
Unknown/Missing	260 (6%)	125 (5%)	135 (8%)	
II. Clinical Factors				
Charlson Index 1 Year Prior				

	Total	Metastatic	Recurrent	p-value
Population Characteristics	N (column %)	N (column %)	N (column %)	
<i>0</i>	2,065 (48%)	1,302 (52%)	763 (43%)	<0.0001
<i>1</i>	1,139 (27%)	629 (25%)	510 (28%)	
<i>2+</i>	1,076 (25%)	555 (22%)	521 (29%)	
Cancer Sequence				
<i>PCa as primary cancer</i>	3,757 (88%)	2,206 (89%)	1,551 (86%)	0.02
<i>Other cancer before PCa</i>	523 (12%)	280 (11%)	243 (14%)	
III. History of Comorbidities				
<i>Myocardial Infarction</i>	74 (2%)	46 (2%)	28 (2%)	0.47
<i>Diabetes</i>	937 (22%)	476 (19%)	461 (26%)	<0.0001
<i>Fracture</i>	104 (2%)	55 (2%)	49 (3%)	0.28
<i>Hyperlipidemia</i>	2,052 (48%)	1,003 (40%)	1,049 (58%)	<0.0001
<i>Hypertension</i>	2,614 (61%)	1,351 (54%)	1,263 (70%)	<0.0001
<i>Stroke</i>	149 (3%)	72 (3%)	77 (4%)	0.01

^aThe quartiles are calculated in all prostate cancer patients diagnosed during 2003–2007.

Table 2

Utilization and sociodemographic and clinical correlates of intermittent androgen deprivation (IADT) among 2,487 metastatic prostate cancer patients aged 66 years and older who started androgen deprivation therapy during 2003–2007 and were followed until December 31, 2010.

	IADT (N=517, row %)	OR (95% C.I.)	p-value (pair-wise test) ^a	p-value (over-all test) ^b
I. Sociodemographic Factors				
<i>Year of ADT initiation</i>				0.13
2003	104 (20%)	1.00		
2004	95 (18%)	0.96 (0.69, 1.34)	0.82	
2005	103 (22%)	1.19 (0.85, 1.67)	0.32	
2006	98 (20%)	1.03 (0.73, 1.46)	0.86	
2007	117 (24%)	1.43 (1.03, 2.00)	0.03	
<i>Age at initiation of ADT</i>				0.89
66–70	103 (22%)	1.00		
71–75	129 (22%)	1.00 (0.73, 1.37)	0.98	
76–80	113 (20%)	0.94 (0.68, 1.30)	0.71	
80+	172 (20%)	0.91 (0.67, 1.23)	0.54	
<i>Race/Ethnicity</i>				0.37
White	443 (21%)	1.00		
African-American	45 (19%)	0.99 (0.70, 1.42)	0.97	
Asian	11 (20%)	0.95 (0.49, 1.85)	0.88	
Other	18 (17%)	0.64 (0.37, 1.10)	0.11	
<i>Married</i>				0.45
No	177 (22%)	1.00		
Yes	340 (20%)	0.92 (0.74, 1.14)	0.44	
<i>Group (Census Tract) Level of High School Graduate Percentage in Quartile^c</i>				0.80
Q1	158 (22%)	1.00		
Q2	144 (23%)	1.04 (0.79, 1.36)	0.78	
Q3	116 (21%)	1.07 (0.80, 1.44)	0.64	
Q4	89 (16%)	0.90 (0.63, 1.29)	0.57	
Unknown/Missing	10 (22%)			
<i>Registry Site</i>				0.003
Pacific	262 (24%)	1.00		
East	97 (17%)	0.61 (0.46, 0.82)	0.001	
Central	112 (18%)	0.70 (0.52, 0.96)	0.03	
Mountain	28 (29%)	1.32 (0.72, 2.42)	0.37	
Unknown/Missing	18 (14%)			
II. Clinical Factors				
<i>Charlson Index 1 Year Prior</i>				0.97
0	288 (22%)	1.00		
1	125 (20%)	0.98 (0.75, 1.28)	0.87	

	IADT (N=517, row %)	OR (95% C.I.)	p-value (pair-wise test) ^a	p-value (over-all test) ^b
2+	103 (19%)	0.96 (0.70, 1.31)	0.80	
Cancer Sequence				0.16
<i>PCa primary</i>	449 (20%)	1.00		
<i>PCa secondary</i>	67 (24%)	1.27 (0.93, 1.74)	0.14	
III. Physician Characteristics				
<i>Specialty</i>				0.46
<i>Urology</i>	389 (20%)	1.00		
<i>All Other</i>	128 (23%)	1.10 (0.86, 1.42)	0.45	
<i>Trained in U.S.</i>				0.86
<i>Yes</i>	432 (21%)	1.00		
<i>No</i>	85 (21%)	1.03 (0.77, 1.36)	0.86	
<i>Years in Practice Since Graduated from Medical School</i>				0.40
<i><=10</i>	15 (27%)	1.00		
<i>11-20</i>	124 (22%)	0.80 (0.40, 1.60)	0.53	
<i>21-30</i>	162 (20%)	0.67 (0.34, 1.33)	0.25	
<i>30+</i>	215 (21%)	0.79 (0.40, 1.56)	0.50	
IV. History of Comorbidities				
<i>Myocardial Infarction</i>				0.62
<i>No</i>	510 (21%)	1.00		
<i>Yes</i>	7 (15%)	0.81 (0.35, 1.91)	0.63	
<i>Diabetes</i>				0.13
<i>No</i>	438 (22%)	1.00		
<i>Yes</i>	79 (17%)	0.78 (0.56, 1.08)	0.13	
<i>Fracture</i>				0.25
<i>No</i>	503 (21%)	1.00		
<i>Yes</i>	14 (25%)	1.51 (0.80, 2.84)	0.20	
<i>Hyperlipidemia</i>				0.14
<i>No</i>	328 (22%)	1.00		
<i>Yes</i>	189 (19%)	0.85 (0.68, 1.06)	0.15	
<i>Hypertension</i>				0.54
<i>No</i>	255 (22%)	1.00		
<i>Yes</i>	262 (19%)	0.93 (0.74, 1.17)	0.54	
<i>Stroke</i>				0.15
<i>No</i>	507 (21%)	1.00		
<i>Yes</i>	10 (14%)	0.61 (0.28, 1.32)	0.21	

^a p-value compared each level of a covariate with the reference level.

^b p-value corresponded to an overall test (comparing all levels among themselves).

^c The quartiles are calculated in all prostate cancer patients diagnosed during 2003–2007.

Table 3

Utilization and sociodemographic and clinical correlates of intermittent androgen deprivation (IADT) among 1,794 recurrent prostate cancer patients aged 66 years and older who started androgen deprivation therapy during 2003–2007 and were followed up to December 31, 2010.

	IADT (n=505, row %)	OR (95% C.I.)	p-value (pair-wise test) ^a	p-value (over-all test) ^b
I. Sociodemographic Factors				
<i>Year of ADT initiation</i>				0.16
2003	31 (24%)	1.00		
2004	84 (30%)	1.20 (0.73, 1.97)	0.47	
2005	79 (27%)	0.93 (0.56, 1.54)	0.77	
2006	139 (26%)	0.92 (0.58, 1.48)	0.74	
2007	172 (31%)	1.28 (0.81, 2.02)	0.29	
<i>Age at initiation of ADT</i>				0.20
66–70	37 (32%)	1.00		
71–75	137 (32%)	1.01 (0.61, 1.69)	0.97	
76–80	135 (29%)	0.88 (0.54, 1.44)	0.61	
80+	196 (25%)	0.75 (0.46, 1.23)	0.25	
<i>Race/Ethnicity</i>				0.69
White	423 (28%)	1.00		
African-American	52 (30%)	1.07 (0.71, 1.62)	0.73	
Asian	14 (32%)	1.22 (0.62, 2.40)	0.56	
Other	16 (25%)	0.74 (0.39, 1.42)	0.37	
<i>Married</i>				0.57
No	180 (29%)	1.00		
Yes	325 (28%)	0.93 (0.73, 1.19)	0.57	
<i>Group (Census Tract) Level of High School Graduate Percentage in Quartile^c</i>				0.29
Q1	142 (30%)	1.00		
Q2	117 (27%)	0.92 (0.68, 1.25)	0.60	
Q3	137 (30%)	1.21 (0.88, 1.65)	0.24	
Q4	97 (25%)	0.92 (0.62, 1.35)	0.66	
Unknown/Missing	12 (28%)			
<i>Registry Site</i>				0.02
Pacific	209 (32%)	1.00		
East	105 (24%)	0.64 (0.46, 0.89)	0.007	
Central	107 (23%)	0.63 (0.45, 0.88)	0.007	
Mountain	33 (33%)	1.00 (0.57, 1.74)	0.99	
Unknown/Missing	51 (38%)			
II. Clinical Factors				
<i>Charlson Index 1 Year Prior</i>				0.01
0	228 (30%)	1.00		
1	157 (31%)	1.13 (0.84, 1.51)	0.43	

	IADT (n=505, row %)	OR (95% C.I.)	p-value (pair-wise test) ^a	p-value (over-all test) ^b
2+	120 (23%)	0.71 (0.51, 0.99)	0.04	
Cancer Sequence				
<i>PCa-primary</i>	453 (29%)	1.00		
<i>PCa- secondary</i>	52 (21%)	0.75 (0.52, 1.05)	0.10	
III. Physician Characteristics				
Specialty				
<i>Urology</i>	451 (28%)	1.00		0.55
<i>All Other</i>	54 (32%)	1.12 (0.77, 1.63)	0.55	
Trained in U.S.				0.47
<i>Yes</i>	434 (29%)	1.00		
<i>No</i>	71 (26%)	0.89 (0.64, 1.23)	0.47	
Years in Practice Since Graduated from Medical School				
<i><=10</i>	9 (29%)	1.00		0.93
<i>11-20</i>	105 (30%)	1.18 (0.44, 3.19)	0.74	
<i>21-30</i>	159 (28%)	1.17 (0.44, 3.11)	0.75	
<i>30+</i>	231 (27%)	1.09 (0.41, 2.89)	0.86	
IV. History of Comorbidities				
Myocardial Infarction				0.99
<i>No</i>	497 (28%)	1.00		
<i>Yes</i>	8 (29%)	1.00 (0.40, 2.49)	0.99	
Diabetes				0.90
<i>No</i>	384 (29%)	1.00		
<i>Yes</i>	121 (26%)	0.98 (0.72, 1.33)	0.90	
Fracture				0.82
<i>No</i>	493 (28%)	1.00		
<i>Yes</i>	12 (24%)	1.09 (0.53, 2.22)	0.82	
Hyperlipidemia				0.24
<i>No</i>	213 (29%)	1.00		
<i>Yes</i>	292 (28%)	1.16 (0.91, 1.47)	0.24	
Hypertension				0.02
<i>No</i>	176 (33%)	1.00		
<i>Yes</i>	329 (26%)	0.75 (0.58, 0.96)	0.02	
Stroke				0.40
<i>No</i>	482 (28%)	1.00		
<i>Yes</i>	23 (30%)	1.27	0.38	

^a p-value compared each level of a covariate with the reference level.

^b p-value corresponded to an overall test (comparing all levels among themselves).

^c The quartiles are calculated in all prostate cancer patients diagnosed during 2003–2007.