



Published in final edited form as:

J Clin Oncol. 2007 December 1; 25(34): 5359–5365.

Urologist characteristics predict use of androgen deprivation therapy for prostate cancer

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Abstract

Purpose—We have previously reported wide variations among urologists in use of androgen deprivation for prostate cancer. Using Surveillance, Epidemiology and End-Results (SEER)-Medicare linked data we examined how individual urologist characteristics influenced use of androgen deprivation therapy.

Methods—Participants included 82,375 men with prostate cancer diagnosed from January 1, 1992, through December 31, 2002, and 2,080 urologists providing care to them. Multi-level analyses were used to estimate likelihood of androgen deprivation use within six months of diagnosis in the overall cohort, a subgroup where use would be of uncertain benefit (primary therapy for localized prostate cancer), and a subgroup where use would be evidence-based (adjuvant therapy with radiation for locally advanced disease).

Results—In the overall cohort of patients, a multi-level model adjusted for patient, tumor and urologist characteristics (board certification, academic affiliation, patient panel size, years since medical school graduation) showed that the likelihood of androgen deprivation use was significantly higher for patients who saw urologists without an academic affiliation. This pattern was also noted when the analysis was limited to settings where androgen deprivation would have been of uncertain benefit. Odds ratios for use in that context were 1.66 (95% CI: 1.27-2.16) for no academic affiliation and 1.45 (95% CI: 1.13-1.85) for minor versus major academic affiliation.

Conclusion—Use of androgen deprivation for prostate cancer varies by the characteristics of the urologist. Patients of non-academically affiliated urologists were significantly more likely to receive primary androgen deprivation therapy for localized prostate cancer, a setting where the benefits are uncertain.

INTRODUCTION

Androgen deprivation therapy has become common for prostate cancer (1,2). Although historically limited to palliation of metastatic prostate cancer, the 1990s witnessed a dramatic growth in use of androgen deprivation across all stages and grades (1).

Part of the rise in use appeared to be evidence-based. Androgen deprivation as adjuvant treatment with radiation for locally advanced or high risk tumors was known to be beneficial for slowing progression of prostate cancer as early as 1992 (3). By 1996, clinical trial evidence of overall survival benefit was available (4), and reflected in National Comprehensive Cancer Network (NCCN) guidelines of the time (5). In contrast, use of androgen deprivation as primary therapy in localized disease was, and is, of uncertain benefit, because no clinical trials have demonstrated its efficacy in that context (6). Neither NCCN or American Urological Association (AUA) guidelines recommended androgen deprivation for localized prostate cancer (5,7), yet its use for that indication more than tripled over the 1990s (1,8).

Given potential harms of androgen deprivation - fractures, sexual dysfunction, reduced quality of life (9), its uncertain benefits in some settings, and substantial financial costs (10), wide geographic variations noted in its use are cause for concern (11,12). Examining the possible contribution of physician practice style to the variation in androgen deprivation use (13), we showed that which urologist a patient with prostate cancer sees is a more important predictor of receipt of androgen deprivation than tumor or patient characteristics (14).

To further explore the role of the urologist, we examined the effect of individual urologist characteristics on the likelihood of androgen deprivation use in a large cohort of men with prostate cancer. We also performed subgroup analyses to test our hypothesis that there would be a relationship between urologist characteristics and the strength of the evidence for the indication to use androgen deprivation, on the likelihood of its use. Specifically, we hypothesized that urologists with board certification and academic affiliation would be more likely to prescribe androgen deprivation for patients where its use would be evidence-based and less likely to prescribe it for patients where its use would be of uncertain benefit.

METHODS

Data Sources

Surveillance, Epidemiology, and End Results (SEER)-Medicare—The SEER program consists of a group of population-based tumor registries in selected geographic areas of the US (15). Medicare is a federal program that covers health services for 97% of persons aged 65 years and older. The information in the two programs has been linked (16). The SEER-Medicare database also contains the Hospital file, which includes information on hospital characteristics such as academic affiliation and is derived from the Provider of Service survey submitted by hospitals to Medicare (17). The SEER-Medicare database version used for this study contains Medicare claims through 2004 and cancer cases from the SEER 11 registries through 2002.

American Medical Association (AMA) Physician Masterfile—The AMA Physician Masterfile contains information on all physicians in the US, regardless of membership in the AMA (18). The information is collected from primary sources, such as medical schools, residency training programs, state licensing agencies, and the American Board of Medical Specialties. Physicians are also surveyed every 3 years regarding their current practice.

Study Subjects

The study included men with incident prostate cancer from 1992 through 2002 that were at least 66 years old at diagnosis (163,613 subjects). To ensure complete information, patients not enrolled in both Medicare Part A and Part B for 12 months before and 6 months following their cancer diagnosis (15,117 cases), who died within 6 months of diagnosis (3,232 cases), were members of an Health Maintenance Organization (36,640 cases), or diagnosed by autopsy or on a death certificate (2,004 cases) were excluded, leaving 106,620 eligible patients.

Physicians providing care to patients within a year of diagnosis were initially identified through encrypted Unique Physician Identifier Numbers (UPIN) on Medicare physician claims. The UPINs were linked to the AMA Physician Masterfile and only physicians with urology as their primary specialty code were selected. Patients who did not see at least one urologist in the year after diagnosis on at least two different days (14,635 patients) were excluded. If a patient saw 2 or more urologists, they were assigned to the urologist with $\geq 75\%$ of urologist visits in the year after diagnosis. If no single urologist accounted for $\geq 75\%$ of the visits, the patient was excluded (9,610 patients).

The primary analysis included all eligible patients, regardless of cancer stage or grade at diagnosis. To test whether the effect of urologist characteristics on use of androgen deprivation was influenced by the strength of the indication for its use, we also performed analyses in two subgroups of patients: those for whom use of androgen deprivation therapy would have been evidence-based and those for whom its use would have been of uncertain benefit. Androgen deprivation together with radiation therapy was known to have salutary effects on disease progression since the early 1990s, although clinical trial evidence of overall survival benefit did not come until 1996 and later (3-5,19,20). The evidence-based group of patients included those receiving radiation who had T3 or T4 tumors without regional or distant metastases (locally advanced), or T2 with high-grade histology (localized but high risk) tumors (n=6,300 patients; n=1,112 urologists). The uncertain-benefit group included patients with T1 or T2 tumors with either low (Gleason score 2-4) or moderate (Gleason score 5-7) grade histology who did not receive radiation or radical prostatectomy (n=18,211 patients; n=1,393 urologists). This group was chosen since there is no clinical trial evidence of efficacy for primary androgen deprivation in this setting (6), and even under theoretical considerations, it is difficult to show survival benefit from any intervention in such patients, due to the slow natural progression and competing risk of death from causes other than prostate cancer (21). In additional analyses, patients were stratified by era of diagnosis into 1992-1995 and 1996-2002 to examine changes in the effect of urologist characteristics over the study period.

Measures

Patient demographic and tumor characteristics were derived from the SEER records in the linked database and used to categorize patients by age, ethnicity, SEER region of residence at the time of diagnosis, year of diagnosis, clinical stage (T1 through T4), and grade (well differentiated - Gleason 2-4; moderately differentiated - Gleason 5-7; poorly or undifferentiated/unknown - Gleason 8-10) (22). Stage was assigned using the SEER Extent of Disease classification system (23). The socio-economic characteristics of each patient were based on the percent of adults with less than 12 years of education and median income of the zip code of residence from the 2000 United States Census data. Comorbidity was measured using an adaptation of the Charlson Comorbidity Index for use with Medicare physician claims data (24,25).

Urologist board certification was available from the AMA based on information from the American Board of Medical Specialties (18). Patient panel size was defined as the number of patients with prostate cancer assigned to each urologist over the study period, and categorized as <15, 15-59, 60-119, and ≥ 120 patients. These categories were pre-specified, and chosen to ensure a reasonable distribution for the number of patients per panel, with cut-offs roughly corresponding to the 2nd quartile, 3rd quartile and 90th percentile. Hospital affiliation with a medical school was available from the SEER-Medicare Hospital file and categorized as no, minor, or major affiliation. Hospitals with major affiliation play an important part in the teaching program of the medical school, hosting a clinical clerkship program, whereas those with minor affiliation only have residency programs and/or occasional student rotations (26). Urologists were categorized as having major or no academic affiliation if all their inpatient

Medicare claims submitted were from a hospital with major or no academic affiliation, respectively. All other urologists were categorized as having minor academic affiliation. Some urologists could not be assigned an affiliation since no inpatient claims were available for them (378 urologists; 594 patients) and were excluded from the main analyses. We performed a multiple imputation procedure (27) to examine the impact of the missing data and found that the results were not substantially changed (data not presented).

The outcome was receipt of androgen deprivation. Androgen deprivation was defined as the receipt of at least one dose of a GnRH agonist (identified through Medicare claims codes used to designate each dose given of injectable medications [1,28]) or orchiectomy (defined by the presence of the Current Procedural Terminology codes or International Classification of Diseases, 9th revision [ICD-9] procedure codes in the Medicare claims) in the first six months following diagnosis of cancer. As such, the study was limited to examining “early” use of androgen deprivation, without consideration for whether patients received androgen deprivation later in their course.

Statistical Analyses

Differences across strata of urologist characteristics in the proportion of patients receiving androgen deprivation were evaluated with chi square statistics. The effect of urologist characteristics on the outcome of use of androgen deprivation was evaluated using hierarchical generalized linear models (29,30). These models account for clustering of patients within urologists. Models entering the urologist, patient and tumor characteristics listed above as independent variables were estimated. Odds ratios (OR) for the use of androgen deprivation for each urologist characteristic were calculated along with 95% confidence intervals (CI). The median urologist rates of androgen deprivation use for various indications were estimated from the models, and plotted by calendar year of diagnosis to show change in use over time.

Analyses were performed with SAS version 9.1 (Cary, NC). All tests of statistical significance were two-sided, with *P* values of less than .05 being considered significant. The study protocol was approved by the local institutional review board at the University of Texas Medical Branch at Galveston.

RESULTS

A total of 2,080 urologists were identified as providing care to 82,375 patients with incident prostate cancer from 1992 through 2002. A majority of urologists were board certified (93.5%), did not have a major academic affiliation (81.5%), and were male (97.8%). Table 1 presents the proportion of patients receiving androgen deprivation within six months of diagnosis by strata of urologist characteristics. Overall, 34.4% of patients received androgen deprivation, with 5.2% receiving orchiectomy, and 29.2% receiving GnRH agonists. A total of 25.7% of urologists provided care to 60 or more patients with incident prostate cancer over the study period. In the overall cohort, a higher proportion of patients of younger, female, non-board certified and non-major academically affiliated urologists received androgen deprivation.

Table 2 presents the results of a hierarchical generalized linear model predicting use of androgen deprivation by patient, tumor and urologist characteristics in the entire cohort of patients, and also stratified by era of diagnosis: 1992-1995 and 1996-2002. The likelihood of androgen deprivation use was significantly higher for patients who saw urologists with no academic affiliation (OR 1.83; 95%CI: 1.52-2.22). The likelihood of androgen deprivation use also increased significantly with increasing patient panel size and years since graduation. When the analysis was stratified by era of diagnosis, the effect of urologist academic affiliation, board certification and panel size strengthened over time. For example, the OR for no academic affiliation increased from 1.30 (95%CI: 1.04-1.63) in 1992-1995 to 2.18 (95%CI: 1.73-2.75)

in 1996-2002. In addition, patients of urologists without board certification were significantly more likely to receive androgen deprivation from 1996-2002.

We then examined the relationship between urologist characteristics and the strength of the indication for use of androgen deprivation. Tables 3 and 4 present hierarchical generalized linear models as performed in Table 2 but limited to the evidence-based (ie. locally advanced or high risk disease receiving radiation) and uncertain benefit (ie. localized, low to moderate grade disease not receiving radiation or radical prostatectomy) subgroups of patients, respectively. In the overall cohort of the evidence-based group, only increasing panel size was a significant predictor of androgen deprivation use. When the analysis was stratified by era of diagnosis, the effect of urologist academic affiliation shifted over time. From 1992-1995, patients of urologists without academic affiliation were less likely to receive androgen deprivation (though not statistically significant), whereas they were significantly more likely to receive it from 1996-2002. This pattern is also evident in Figure 1, which shows the median urologist rate of androgen deprivation use plotted over time comparing urologists with major academic affiliation to those without any affiliation.

In the uncertain benefit group, patients of urologists without academic affiliation were significantly more likely to receive androgen deprivation. This effect appeared to strengthen over time when the analysis was stratified by era of diagnosis. Figure 2 shows median urologist rate of androgen deprivation use plotted over time comparing urologists with major academic affiliation to those without any affiliation. Use of androgen deprivation by academic urologists was generally flat whereas use by urologists without academic affiliation doubled over the study period.

DISCUSSION

The main finding of this study is that androgen deprivation use for prostate cancer varies by the characteristics of the urologist. Overall, patients of urologists who were not academically affiliated, who had a larger patient panel size or who had graduated less recently were significantly more likely to receive androgen deprivation. Furthermore, patients of non-academically affiliated urologists were significantly more likely to receive primary androgen deprivation therapy for localized prostate cancer, a setting where the benefits are uncertain.

How did our findings compare to our initial hypotheses? Patients of non-board certified urologists were significantly more likely to receive androgen deprivation in the uncertain benefit group in unadjusted analyses (Table 1) although this finding did not achieve statistical significance in the multivariable analyses (Table 4). The increased use of androgen deprivation by non-board certified urologists in the evidence-based group from 1992-1995 is difficult to explain, although this effect was abolished in the period from 1996-2002. The effect of urologist academic affiliation on evidence-based use showed an interesting pattern (Figure 1). The higher use of androgen deprivation in this context by academic urologists from 1992-1995 is consistent with what is known about early adopters, who tend to be providers that are involved in the testing of new therapies (31). Following publication of the clinical trials, use in this setting increased dramatically for all groups of urologists, but with a significantly higher rate for urologists without academic affiliation. This may be due to more cautious or selective use of androgen deprivation by academic urologists in response to the evidence (32). In addition, factors other than evidence of benefit may have influenced use of androgen deprivation by urologists without academic affiliation. Financial incentive might play a greater role for non-academically affiliated urologists, who may be more likely paid on a fee-for-service rather than salaried basis. Through the 1990s, androgen deprivation use in the form of GnRH agonists allowed a substantial profit for every dose administered, and formed a substantial portion of private practice urologists' income (33,34). Physicians in academic settings may have more

time for discussion of risks and benefits, which could lead to lower use of androgen deprivation in settings where its benefits are uncertain (32). Finally, academic physicians may be less influenced by pharmaceutical industry marketing of GnRH agonists (35).

There are limitations to this study. Only men 66 years and older were included, and use of androgen deprivation in health maintenance organizations could not be examined. Some study exclusions may have limited generalizability of the results. For instance, some patients receiving care from multiple urologists were excluded (nearly 10% of our initial study sample). The unadjusted rate of androgen deprivation use among those patients was 37%, versus 34% in the final study sample. Despite the population-based nature of the study, statistical power was limited for some of the stratified analyses rendering confidence intervals too wide for meaningful interpretation of some results. Assignment of urologist academic affiliation, based on Medicare claims, may have been imperfect. However, misclassification would tend to bias the results to the null, so that significant associations should still be valid. Finally, some potentially relevant variables, such as prostate-specific antigen (PSA) levels, were not available. However, after adjustment for other important tumor variables such as stage and grade, it is unlikely that there would be substantial differences in PSA levels across urologist characteristics. Furthermore, it might be expected that patients with higher risk disease would tend to see academically affiliated urologists. This should have led to more, rather than the less use of androgen deprivation noted among academically affiliated urologists in this study.

What implications do our study findings have for optimizing use of androgen deprivation therapy? It is important first to note that use of androgen deprivation in settings of uncertain benefit was common even among urologists with a major academic affiliation (Table 1). If all patients with prostate cancer saw academic urologists there would only be an estimated 10.5% reduction in the number that would be prescribed androgen deprivation in settings of uncertain benefit. Nevertheless, the significant associations noted in this study between urologist characteristics and use of androgen deprivation still provide insight into what efforts may be successful for improving the use of this therapy. The effects of academic affiliation suggest that provider education should be a priority. Current practice guidelines for management of prostate cancer may not be sufficient. For example, the NCCN guidelines on the management of prostate cancer are primarily composed of algorithms describing current standards of care (5). Use of boundary guidelines, which specifically define appropriate and inappropriate use of therapy, may be more helpful (36). Ongoing clinical trials should eventually help clarify the optimal role of androgen deprivation therapy, possibly reducing variations in its use (37,38). In addition, the reductions in reimbursement for GnRH agonists brought about by the Medicare Modernization Act in 2003 should help reduce discretionary use of androgen deprivation. Some discretion in use of androgen deprivation in settings where its benefits are uncertain is expected, and use in that context may not necessarily be inappropriate. Nevertheless, the significant differences in androgen deprivation use as a function of urologist characteristics are cause for concern. Efforts directed at reducing the variation in use of androgen deprivation therapy among urologists are needed.

ACKNOWLEDGMENTS

This study used the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. The authors acknowledge the efforts of the Applied Research Program, NCI; the Office of Research, Development and Information, CMS; Information Management Services (IMS), Inc.; and the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of the SEER-Medicare database.

Role of the Funding Source

This work was supported in part by grants (RO1CA116758, P50CA105631, R24HS011618) from the Public Health Service. The funding bodies had no role in data extraction and analyses, in the writing of the manuscript, or in the decision to submit the manuscript for publication.

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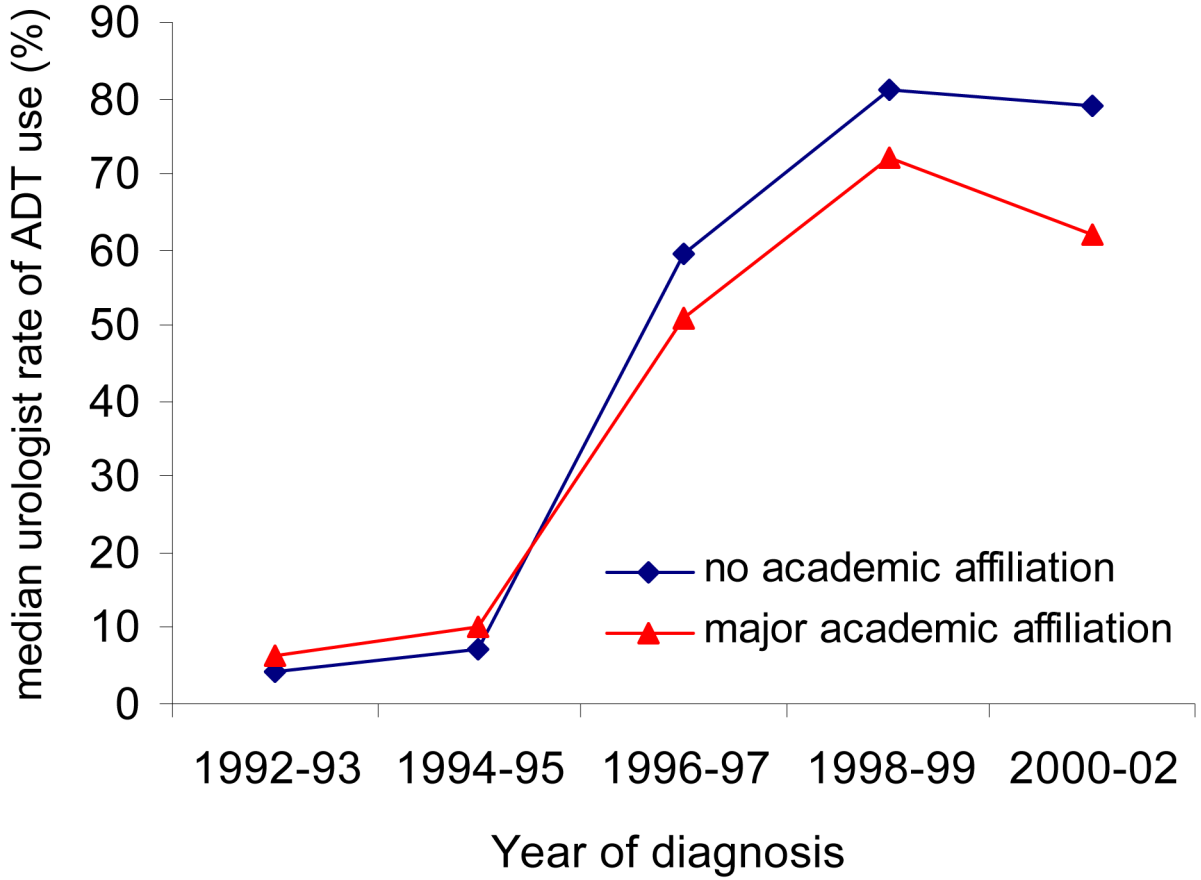


Figure 1. Urologist-specific rates of androgen deprivation use (ADT) in the evidence-based group of patients, adjusted for patient characteristics, were estimated from hierarchical generalized linear models for each era of diagnosis (1992-93, 1994-95, 1996-97, 1998-99, 2000-02). The median urologist-specific rates for urologists with major versus no academic affiliation were plotted for each era of diagnosis.

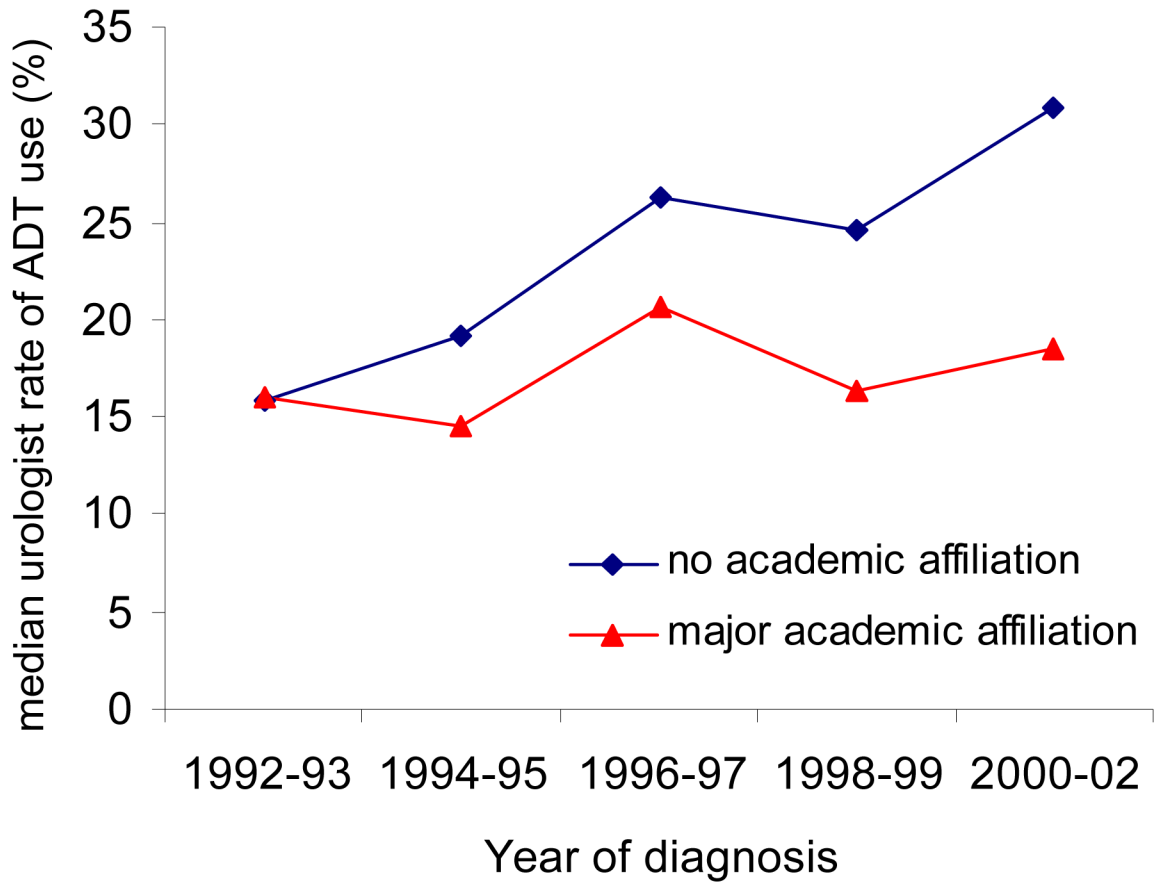


Figure 2.

Urologist-specific rates of androgen deprivation use (ADT) in the uncertain benefit group of patients, adjusted for patient characteristics, were estimated from hierarchical generalized linear models for each era of diagnosis (1992-93, 1994-95, 1996-97, 1998-99, 2000-02). The median urologist-specific rates for urologists with major versus no academic affiliation were plotted for each era of diagnosis.

Table 1

Proportion of patients receiving androgen deprivation by strata of urologist characteristics

Urologist Characteristics	Category	Number of urologists, n (%)	Overall cohort (n=82,375)	Percent of patients receiving androgen deprivation, % based group (n=6,300)	p-value ^d	Uncertain Benefit group (n=18,211)	p-value ^d
Total		2080	34.4	42.7		32.4	
Age (years)	< 45	780 (37.5)	34.4	42.7	<0.001	32.4	0.094
	45 - 54	609 (29.3)	35.5	49.2		33.0	
	55 - 64	564 (27.1)	32.5	37.0		31.3	
Gender	≥ 65	127 (6.1)	33.9	32.7		35.3	
	Female	45 (2.2)	39.0	52.2	0.030	25.6	0.116
Years Since Medical School Graduation	Male	2035 (97.8)	34.4	42.6		32.5	
	< 15	586 (28.2)	35.6	50.0	<0.001	35.0	<0.001
Board Certification	15 - 24	569 (27.4)	34.8	45.8		30.7	
	25 - 34	630 (30.3)	33.1	39.6		31.4	
	≥ 35	295 (14.2)	35.1	33.9		36.5	
Academic Affiliation ^b	Yes	1945 (93.5)	34.1	42.7	<0.001	32.0	<0.001
	No	135 (6.5)	38.6	42.9		38.6	
Panel size (no. of patients)	Major	316 (18.6)	30.2	41.3	<0.001	29.0	0.002
	Minor	832 (48.9)	34.3	42.3		33.0	
	No affiliation	554 (32.6)	36.5	44.0		32.4	
Panel size (no. of patients)	< 15	1058 (50.9)	30.8	35.2	<0.001	27.6	0.026
	15 - 59	486 (23.4)	33.1	36.4		32.1	
	60 - 119	334 (16.0)	35.6	45.1		32.3	
	≥ 120	202 (9.7)	34.4	44.4		33.1	

^a p-value from chi-square test for differences in proportion of patients receiving androgen deprivation across strata for each characteristic

^b missing data on 378 urologists

Table 2
Urologist characteristics as predictors of androgen deprivation use in multilevel models

Urologist Characteristics	Category	Adjusted odds ratios for use of androgen deprivation					
		OR	Overall, ^{ab} (95% CI)	OR	1992-1995, ^{ac} (95% CI)	OR	1996-2002, ^{ad} (95% CI)
Years Since Graduation Board Certification	Every 5 years	1.03	1.00,1.06	1.00	0.97,1.03	1.03	0.99,1.07
	Yes	1.00		1.00		1.00	
Academic Affiliation	No	1.26	0.99,1.60	1.16	0.88,1.52	1.36	1.01,1.83
	Major	1.00		1.00		1.00	
	Minor	1.51	1.27,1.81	1.27	1.03,1.56	1.60	1.29,1.99
	No affiliation	1.83	1.52,2.22	1.30	1.04,1.63	2.18	1.73,2.75
Panel Size	< 15	1.00		1.00		1.00	
	15 - 59	1.26	1.07,1.48	1.10	0.89,1.36	1.39	1.13,1.71
	60 - 119	1.41	1.18,1.67	1.12	0.90,1.39	1.69	1.36,2.10
	≥120	1.44	1.19,1.76	1.13	0.89,1.43	1.76	1.38,2.25

^aBased on hierarchical generalized linear model with patient age, comorbidity, ethnicity, SEER region, tumor stage, grade, year of diagnosis, zip code education, and zip code poverty entered as "level 1" variables and urologist characteristics entered as "level 2" variables.

^bn=81,781 patients; n=1,702 urologists

^cn=36,113 patients; n=1,500 urologists

^dn=46,262 patients; n=1,668 urologists

Urologist characteristics as predictors of androgen deprivation use in multilevel models in the evidence-based group of patients

Table 3

Urologist Characteristics	Category	OR	Adjusted odds ratios for use of androgen deprivation		
			Overall, ^{ab} (95% CI)	1992-1995, ^{ac} (95% CI)	1996-2002, ^{ad} (95% CI)
Years Since Graduation Board Certification	Every 5 years	0.97	0.92,1.02	0.98	0.94
	Yes	1.00		1.00	1.00
Academic Affiliation	No	1.19	0.77,1.83	2.50	0.94
	Major	1.00		1.00	1.00
	Minor	1.00	0.73,1.38	0.75	1.22
	No affiliation	1.09	0.77,1.55	0.63	1.58
Panel Size	< 15	1.00		1.00	1.00
	15 - 59	1.28	0.83,1.96	1.49	1.15
	60 - 119	1.70	1.11,2.61	1.97	1.59
	≥ 120	1.95	1.25,3.06	1.96	2.12

^a Based on hierarchical generalized linear model with patient age, comorbidity, ethnicity, SEER region, tumor stage, grade, year of diagnosis, zip code education, and zip code poverty entered as "level 1" variables and urologist characteristics entered as "level 2" variables.

^b n=6,300 patients, n=1,112 urologists overall; smallest sample size n=254 patients in panel size < 15 stratum, n=64 urologists in no board certification stratum

^c n=2,769 patients, n=812 urologists overall; smallest sample size n=116 patients in panel size < 15 stratum, n=43 urologists in no board certification stratum

^d n=3,531 patients, n=866 urologists overall; smallest sample size n=134 patients in panel size < 15 stratum, n=47 urologists in no board certification stratum

Urologist characteristics as predictors of androgen deprivation use in multilevel models in the uncertain benefit group of patients

Table 4

Urologist Characteristics	Category	OR	Adjusted odds ratios for use of androgen deprivation		
			Overall, ^{ab} (95% CI)	1992-1995, ^{ac} (95% CI)	1996-2002, ^{ad} (95% CI)
Years Since Graduation Board Certification	Every 5 years	1.03	0.98,1.07	0.98,1.09	1.03
	Yes	1.00			1.00
Academic Affiliation	No	1.35	0.98,1.86	0.85,1.92	1.47
	Major	1.00			1.00
	Minor	1.45	1.13,1.85	0.93,1.75	1.49
	No affiliation	1.66	1.27,2.16	0.86,1.71	1.84
Panel Size	< 15	1.00			1.00
	15 - 59	1.20	0.92,1.58	0.74,1.67	1.28
	60 - 119	1.19	0.90,1.57	0.69,1.59	1.30
	≥ 120	1.20	0.89,1.62	0.82,1.94	1.23

^aBased on hierarchical generalized linear model with patient age, comorbidity, ethnicity, SEER region, tumor stage, grade, year of diagnosis, zip code education, and zip code poverty entered as "level 1" variables and urologist characteristics entered as "level 2" variables.

^bn=18,211 patients, n=1,393 urologists overall; smallest sample size n=702 patients in panel size < 15 stratum, n=94 urologists in no board certification stratum

^cn=7,299 patients, n=1,047 urologists overall; smallest sample size n=287 patients in panel size < 15 stratum, n=69 urologists in no board certification stratum

^dn=10,912 patients, n=1,156 urologists overall; smallest sample size n=415 patients in panel size < 15 stratum, n=70 urologists in no board certification stratum