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Ruben Guang Wei Quek Date

Influence of Physician Characteristics on the Treatment of Prostate Cancer

By

Ruben Guang Wei Quek
Doctor of Philosophy

Health Services Research and Health Policy

Joseph Lipscomb, Ph.D.
Advisor

Katherine S. Virgo, Ph.D., M.B.A.
Committee Member

Kenneth M. Portier, Ph.D.
Committee Member

Kevin C. Ward, Ph.D., M.P.H.
Committee Member

Viraj A. Master, M.D., Ph.D.
Committee Member

Accepted:

Lisa A. Tedesco, Ph.D.
Dean of the James T. Laney School of Graduate Studies

Date

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By

Ruben Guang Wei Quek
M.Phil., University of Cambridge, 2008
B.Eng., Imperial College London, 2007

Advisor: Joseph Lipscomb, Ph.D.

An abstract of
A dissertation submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
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Abstract

Influence of Physician Characteristics on the Treatment of Prostate Cancer

By Ruben Guang Wei Quek

This dissertation is prepared in light of the ongoing debate about prostate cancer overtreatment, with its attendant implications for patient outcomes and U.S. health care expenditures. Physician characteristics and changes in drug reimbursement rates have been shown to influence practice patterns regardless of clinical guidelines and patient, clinical or sociodemographic factors. This dissertation consists of three essays investigating the effect of physician characteristics on prostate cancer treatment and referral patterns.

The first essay examined the association between urologists' practice affiliations with medical schools and guideline discordant use of primary medical androgen deprivation therapy (ADT) for clinically localized prostate cancer patients, before and after the 2003 Medicare Modernization Act (MMA)'s reductions in ADT reimbursement rates. The odds of patients receiving guideline discordant ADT started to decrease before the MMA. In addition, patients treated by urologists without medical schools affiliations are significantly more likely to receive guideline discordant ADT before and after the passage of the MMA.

The second essay investigated the impact of the urologist on the likelihood that patients with locoregional prostate cancer would consult a radiation oncologist. Patients with locoregional prostate cancer who receive their diagnostic biopsy from urologists practicing in non-institutional settings and/or those who consulted older urologists are significantly more likely to eventually consult a radiation oncologist.

For patients with low-risk clinically localized prostate cancer, the third essay explored the association between patients' clinical, sociodemographic and radiation oncologists' characteristics have on the likelihood that patients received combined external beam radiation therapy and brachytherapy– a treatment regimen at variance with clinical guidelines. Patients' geographic and sociodemographic factors are significantly associated with guideline discordant radiation therapy for patients diagnosed with low-risk clinically localized prostate cancer. Which radiation oncologist a patient consults is important in determining whether they receive combined radiation therapy.

Prostate cancer patients receiving treatments at variance to guidelines and especially those receiving more care than guidelines recommend may be faced with unnecessary health care costs coupled with increased risks for genitourinary and/or gastrointestinal toxicity and decreased quality of life. Efforts directed at reducing guideline discordant treatment and referral patterns among prostate cancer patients are needed.

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NOTE: A version of Chapter 7 of this dissertation was published in 2013. See: Quek, R. G. W. et al. (2013). Determinants of the combined use of external beam radiotherapy and brachytherapy for low-risk, clinically localized prostate cancer. *Cancer*. Article First Published Online 31 JUL 2013. DOI: 10.1002/cncr.28258 © 2013 American Cancer Society.

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CHAPTER 1 BACKGROUND

Introduction – Prostate Cancer

Among U.S. men, prostate cancer is the most common non-skin cancer. About 1 man in 6 will be diagnosed with prostate cancer during his lifetime[1]. Prostate cancer occurs mainly in older men. It is also the second leading cause of cancer death in American men, behind only lung cancer[2]. See Figure 1.1 for a breakdown in trends of death rates among males across different cancers. About 1 man in 36 will die of prostate cancer[1]. Approximately 90% of men with newly diagnosed prostate cancer have disease confined to the prostate gland (i.e. clinically localized prostate cancer)[1]. Estimated 2010 U.S. national costs for prostate cancer care ranks fifth (USD 11.85 billion) among cancer types for men and women[2].

Prostate Cancer Treatment Modalities[3]

Common treatment options for prostate cancer include watchful waiting (expectant management or active surveillance), surgery to remove the prostate (i.e. radical prostatectomy), radiation therapy (e.g. external beam radiation therapy (EBRT), interstitial brachytherapy), and androgen deprivation therapy [e.g. surgical removal of the testes (i.e. orchiectomy), use of Luteinizing Hormone Releasing Hormone (LHRH) agonists]. Patient treatment decisions can potentially incorporate physician recommendations, estimated likelihood of cancer progression, treatment location, costs, curative potential and side effects (including adverse toxicity effects and changes in quality of life). Overall survival rates (Figure 1.2) and treatment associated complications (Figure 1.3) vary across treatment modalities. A systematic review commissioned by the

[1] http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-key-statistics
[2] CA Cancer J Clin. 2013;63(1):11-30
[3] Ann Intern Med. 2008;148(6):435-48

Agency for Healthcare Research & Quality concluded that insufficient high quality evidence exists to support any given treatment modality over another.

Physicians Influence[4]

The literature regarding prostate cancer treatment options is often contradictory and confusing even to clinical experts. Thus, there is no clear cut indication as to which treatment is best for many men. Without a gold standard for prostate cancer treatment, patients are dependent on physicians to guide them through the difficult decision making process.

The professional uncertainty hypothesis[4] states that variation in clinical practice occurs to a large extent because of differences among physicians in their evaluation of their patients or in their belief in the value of meeting patient needs. In cases where uncertainties in optimal treatment course exists and where information asymmetry occurs between physicians and patients, characteristics of physicians rather than specific characteristics of patients may influence and determine the eventual medical intervention received by the patient. Variations in physician practice may be influenced by a complex interaction of self-interest, concern for their individual patients, and regard for the well-being of society at large.

Clinical Practice Guidelines

Clinical practice guidelines serve as a guide for physicians to improve quality of care by decreasing inappropriate variation and expediting the application of evidence-based medicine to everyday medical practice. Clinical practice guidelines are systematically developed, mostly with clinical evidence, to assist physicians and patients in making decisions about appropriate health care for specific clinical scenarios. The successful

[4] Med Care. 2002;40(11):1016-35, JAMA. 1999 20;282(15):1458-65

adoption of guidelines is known to improve quality of care[5]. Nonetheless, clinical guidelines have been shown to have limited impact on physician behavior and there are a myriad of reasons associated with noncompliance[6,7]. See Figure 1.4 for barriers to physicians' adherence to clinical practice guidelines in relation to behavior change.

Even with strong level-1 clinical evidence, there is a considerable lag time in translation from clinical evidence discovery to clinical practice. The director of the Agency for Healthcare Research and Quality mentioned in her 2006 testimony before the U.S. Joint Economic Committee that there is a "17-year time lag between discovery and when most Americans benefit from that discovery"[8].

Physician Practice Settings[9,10]

Studies have shown that variation in the primary treatment of prostate cancer can be influenced by physician practice setting. Landon et al. found that practice setting was the most consistent predictor of the physician treatment choices for specific clinical situations. Hughes et. al. used four categories to capture important differences in physician practice setting characteristics. Practice setting can vary by ownership status (e.g. federally owned, privately owned), practice type (e.g. hospital, clinic), financial reimbursement model (e.g. managed care, fee-for-service) and practice size (e.g. solo, partnership, group). In addition, another category that is relevant in describing physician practice settings is academic affiliation. For example, hospitals with a major academic affiliation may play an important role in the teaching program of the medical school by hosting a clinical clerkship program, residency program and student rotations. Physicians who practice within such a setting would have responsibilities that include

[5] Ann Intern Med. 1990;30:709-714.
[6] JAMA. 1999 20;282(15):1458-65
[7] NEngl JMed. 1989;321:1306-1311.
[8] http://www.hhs.gov/asl/testify/t060510a.html
[9] Arch Fam Med. 1995;4(9):759-65.
[10] J Clin Oncol. 2010;28(7):1117-23, Medical Care, 2001, 39(8), 889-905

teaching and clinical research, in addition to patient care. Previous studies have indicated that higher quality of care and better guideline compliance are found in academic settings compared with non-academic settings[11].

Physician Financial Incentives

Financial incentive theory has been developed and used in multiple disciplines; psychologists have found that characteristics of individual providers may influence their responses to incentives[12]. Physician financial incentives are associated with many market occurrences (eg. drug price and reimbursement changes)[13], social aspects of health care (eg. utilization review, peer pressure, practice culture)[14] and can vary across physician organizations and practices (eg. medical groups, independent practice associations, physician hospital organizations)[15].

Physician financial incentives stemming from the Medicare fee-for-service (FFS) payment system creates an inherent pressure within the health care system towards overuse of medical care[16] and may have induced overtreatment. The agency theory[17] suggests that financial incentives are most likely to influence behaviors when there is a clear and direct link between behaviors and rewards; conflict of interest and effect on health care utilization could arise when the physician acts as both the agent (patient adviser) and seller of health care. Moreover, previous research has shown that financial incentives are most likely to have an effect on physician behavior in cases in which

[11] J Clin Oncol. 2008;26(22):3735-42, N Engl J Med 2005; 353:265-274, Milbank Q. 2002;80(3):569-93, v., JAMA. 2000;284(10):1256-62.
[12] Arch Inter Med, 1985, 145(7), 1257-1259
[13] Med Care, 1983, 21(8), 803-815
[14] Med Care, 2004, 42(3), 297-302
[15] Medical Care Research and Review, 2004, 61(3), 37s-68s
[16] JAMA. 1999 20;282(15):1458-65
[17] Am Econ Rev, 1963, 53(5), 941-973, Aca Mgt J, 1988, 31(3), 488-511

medical uncertainty exists, as opposed to cases in which lifesaving care is paramount[18]. The degree of financial incentives across different practice settings also play a role in the utilization of health care[19].

Physicians are reimbursed differently depending on their practice settings; research has shown that salaried versus FFS reimbursement by practice setting influences physician behavior[20]. Similarly, physicians practicing within FFS treatment settings may have a financial incentive to deliver more care than is consistent, whereas physicians on a salary may not have such an incentive[21]. Evidence has shown that patients treated by urologists practicing in non-academic settings (who are usually reimbursed on a FFS basis, whereas academic urologists are usually salaried) were 60% more likely to receive hormonal therapy in cases of uncertain benefit[22]. Jacobson et al. showed that regional variation in reimbursement for chemotherapeutics in the 1990s did not affect the overall utilization rate of chemotherapy for metastatic breast, lung or gastrointestinal tumors, but it did affect the selection of chemotherapeutic agents. Specifically, highly reimbursed physicians were more likely to prescribe more expensive chemotherapy agents[23].

Even when individuals are instructed about the potential for financial ties to affect behavior, and they attempt to remain impartial, their decisions may be influenced by an unintentional and unconscious self-serving bias[24]. There is also growing evidence that physicians with ownership interests refer patients for procedures more frequently than

[18] Med Care, 2004, 42(3), 297-302
[19] J Gen Int Med, 2006, 21, S9-S13, Am J Pub Hlth, 1998, 88(11), 1699-1701
[20] Ped, 1987, 80(3), 344-350
[21] NEJM 1986, 315(1), 59-61
[22] JCO 2007;25(34):5359-5365
[23] Health Affairs 2006;98(12):839-845
[24] JAMA, 2003;290:252-255

those without financial conflicts[25]. This has been demonstrated across multiple diagnostic and therapeutic areas including diagnostic imaging[26], prostate surgical pathology services[27], orthopedic surgical procedures[28], radiation therapy[29], physical therapy and rehabilitation[30] and coronary revascularization[31]. The American Medical Association (AMA) Council on Ethical and Judicial Affairs called on physicians to disclose financial relationships to patients because "arrangements might put patient's medical interest in conflict with the physician's financial interest"[32].

Other Physician Characteristics

There are additional physician characteristics that may influence or affect physician behaviors (e.g. physician experience, workload and gender). The acquisition of expertise in clinical practice is commonly thought to be gained through extensive experience. Years spent in medical practice and age may be indicators of physician experience. Experience may also have an impact on the treatment choices related to clinical reasoning and decision making[33]. In addition, there are inherent differences in workload (e.g. patient volume) within different physician practice settings, and there is variation in physician preferences to work in specific settings. For example, oncologists in private practice generally have a higher patient volume[34]. Gender differences exist within medical practice with male physicians commanding higher income and working longer

[25] The New Yorker, June 1 2009, Med Care 2008;46:732-737,
[26] Radiology 245:2:2007 517-522
[27] Health Aff 31:4:2012 741-749
[28] Arch Surg 145:8:732-738
[29] NEJM 1992:327:21:1497-1501
[30] J Health Econ 14:1995:263-289
[31] JAMA 2007:297:9:962-968
[32] American Medical News. Dec 1 2008 ed
[33] Social Science & Medicine, 70(11), 1728-1736.
[34] Cancer, 115(17), 3848-3857

hours[35]. Physicians may be influenced differently by the financial incentives inherent within practice settings and therefore influence study outcomes.

Patient Characteristics

Both overall health status (e.g. number of non-cancer comorbidities) and cancer severity (i.e. extent of the spread of cancer and the likelihood of cancer recurrence) will affect the treatment and/or referral patterns associated with the physician. In particular, patients with certain health status and cancer severity may end up in certain physician settings (e.g. hospital versus outpatient clinic) best suited to treat patients with those specific clinical characteristics. In addition, race/ethnicity and age may genetically predispose patients to prostate cancer. Socioeconomic status may be correlated with the awareness and directly related to the ability to afford available treatment options and therefore may influence the patient's decisions in receiving specific treatment, being referred to other specialists and/or choice of treatment settings. Likewise, where the patient lives (rural versus non-rural) may affect his choice of physicians. For example, Medicare statistics showed that states with the highest annual per capita spending on urology drugs generally had the greatest volume reductions in 2005 after Medicare reimbursement reductions for Part B drugs[36]. This suggests that patient's geographic locale may affect treatment and referral outcomes.

In Chapter 2, the relationship between patient and physician characteristics, and treatment outcomes will be represented and explained using a conceptual model.

[35] Work and Occupations, 27(4), 464-499
[36] Impact of Changes in Medicare Payments for Part B Drugs, MEDPAC 2007

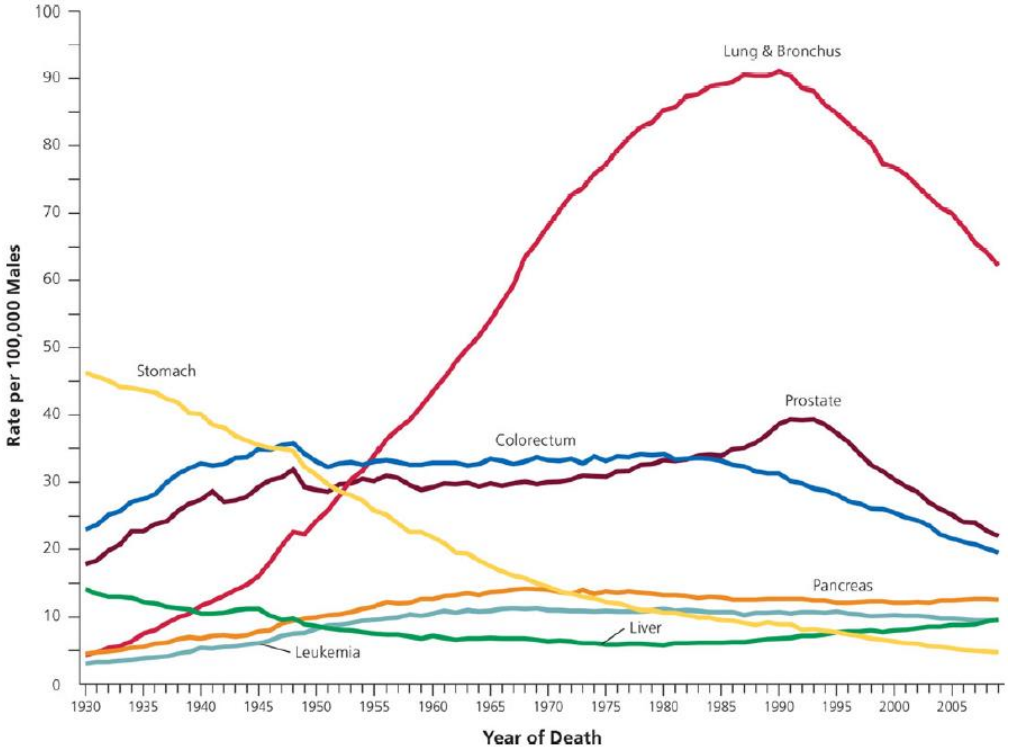
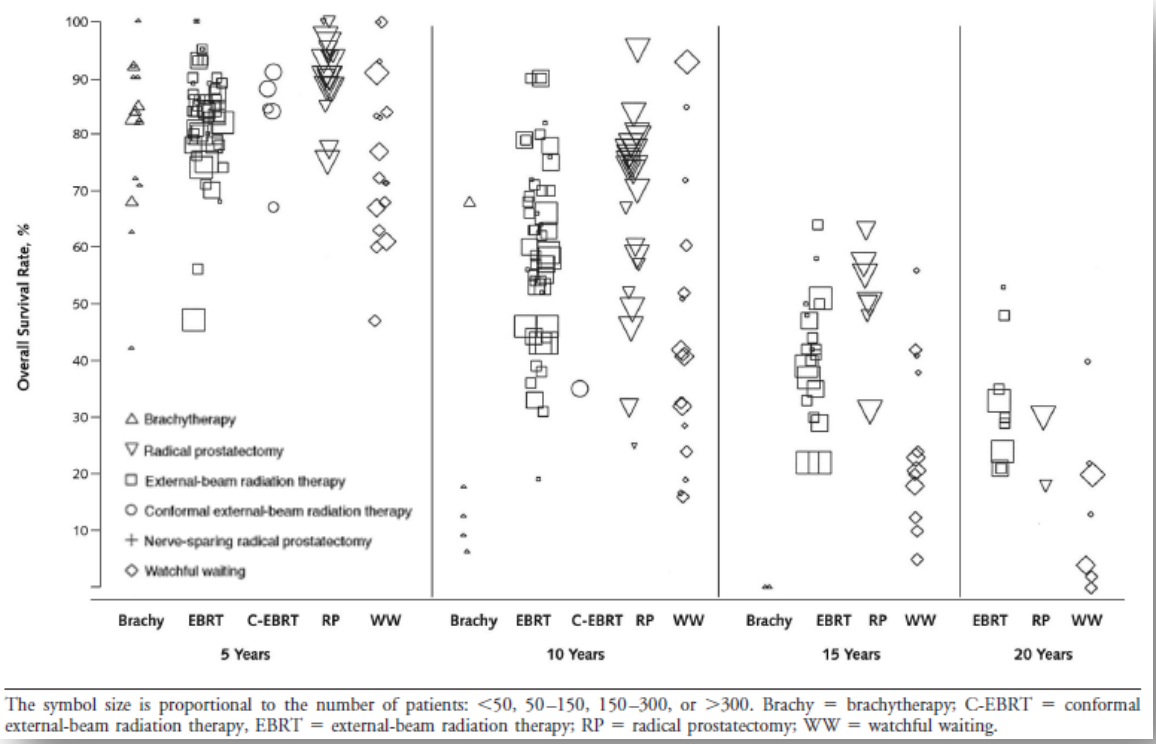


Figure 1.1 Trends in death rates among males for selected cancers, United States, 1930 to 2009. Rates are age adjusted to the 2000 US standard population[37].

[37] CA Cancer J Clin. 2013;63(1):11-30



The symbol size is proportional to the number of patients: <50, 50–150, 150–300, or >300. Brachy = brachytherapy; C-EBRT = conformal external-beam radiation therapy, EBRT = external-beam radiation therapy; RP = radical prostatectomy; WW = watchful waiting.

Figure 1.2 Overall survival at time points by treatment, from non-randomized studies[38]

[38] Ann Intern Med. 2008;148(6):435-48

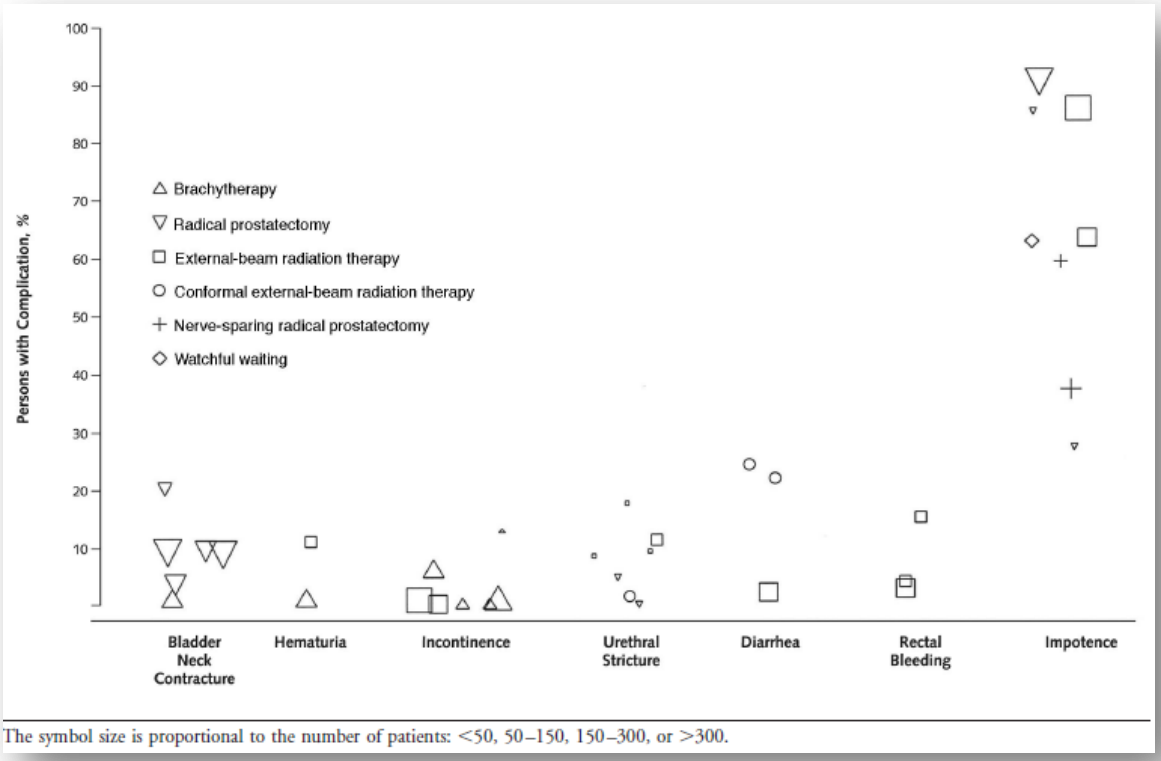


Figure 1.3 Complications of different prostate cancer treatment modalities from non-randomized studies[39]

[39] Ann Intern Med. 2008;148(6):435-48

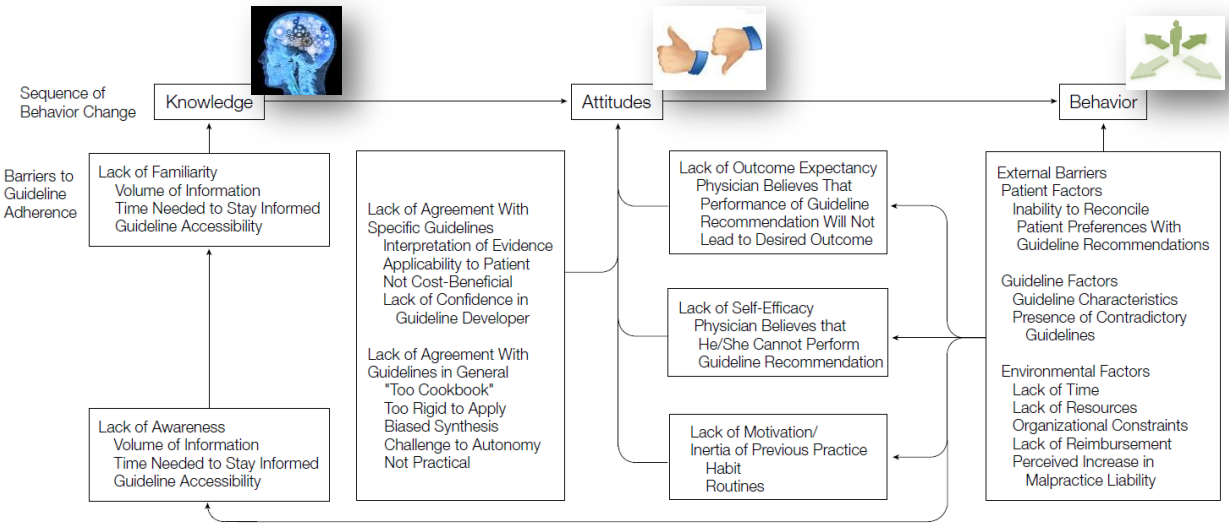


Figure 1.4 Barriers to physicians' adherence to clinical practice guidelines in relation to behavior change[40]

[40] JAMA. 1999 20;282(15):1458-65

CHAPTER 2 CONCEPTUAL MODEL AND HYPOTHESES TESTING

Conceptual Model

The framework developed by Frølich et al.[1] (Figure 2.1) to examine the determinants of providers' responses and incentives serves as a foundation for the conceptual model used for all three essays of this dissertation (Figure 2.2). By adapting Andersen's et al.[2] behavioral model, the Frølich et al. framework integrates theoretical considerations of incentives in health care and factors that influence provider behavior. It also includes explicit recognition of how key factors such as pre-existing traits of providers, characteristics of payment models (eg. FFS or capitation) and patient characteristics can predispose, enhance or mitigate response to different stimuli.

Frølich et al. looked at how a stimulus (e.g. a Pay-For-Performance program) may be affected by environmental variables (e.g. financial characteristics of environment) and how the stimulus may ultimately lead to changes in provider behavior and outcomes (e.g. clinical performance). By adapting this framework, multiple determinants (e.g. patient clinical and sociodemographic characteristics, physician characteristics and the influence of financial incentives inherent within the physician practice settings) of the outcomes of interest will be examined.

Construct Measurement

The conceptual model used in this dissertation is made up of several components. A focal relationship, defined by Aneshensel[3], as the relationship of how "one construct is related to another by demonstrating that an empirical association between two variables

[1] Health Policy, 2007, 80(1), 179-193
[2] Journal of Health and Social Behavior, 36(1), 1-10
[3] Carol S. Aneshensel, Theory-based Data Analysis for the Social Sciences, Introduction to Theory-Based Data Analysis, 2002

is explained, at least in part, by theoretical processes and that alternative explanations do not account for the observed association", forms the most central relationship in the conceptual model. A full *mediator* conveys the entire impact of the focal independent variable on the dependent variable.[3] A *moderator* modifies the effect of the focal independent variable on the dependent variable.[3] A *confounder* may explain the focal relationship in cases where variables in the focal relationship share a common cause.[3] A detailed explanation and discussion of different components of conceptual models can be found in Carol S. Aneshensel's *Theory-based Data Analysis for the Social Sciences, Introduction to Theory-Based Data Analysis*.

The physician financial incentives will serve as a full *mediator* for the focal relationship (in Figure 2.2). Physician financial incentives are derived indirectly from how physicians are paid, which is assumed to be dependent indirectly on the physicians' level of medical school affiliation. The medical school affiliation of the physician will therefore serve as a key independent construct used for all three essays of this dissertation.

For the first essay, the Medicare Modernization Act (MMA) of 2003 will serve as a *moderator* for the relationship between physician financial incentives and the outcome of interest (i.e. guideline discordant primary utilization of medical androgen deprivation therapy (ADT)). The MMA reduced the profit margins associated with the use of ADT through the reduction of Medicare reimbursement rates in 2004 and 2005. Therefore, the MMA is expected to weaken the positive relationship between physician financial incentives and ADT utilization. Further information about the first essay can be found in Chapter 5.

Patient clinical and sociodemographic characteristics used in all three essays of this dissertation represent *confounders* in the conceptual model (Figure 2.2). Likewise,

physician characteristics that affect the focal relationships analyzed in all three essays of this dissertation will also act as *confounders*. Because of the complexity and difficulty in capturing and measuring all physician financial incentives, they will not be assessed directly in this dissertation. See Table 2.1 for specific details describing the operationalization of the measures (i.e. independent variables), moderator (i.e. only for the first essay: implementation of the MMA of 2003) and confounders (i.e. patient clinical and sociodemographic characteristics, physician characteristics) used for all three essays of this dissertation.

Testable Hypotheses

Specific details regarding the background and rationale for the hypotheses tested in the first, second, and third essays of the dissertation can be found in Chapters 5, 6 and 7 respectively. A summary of the hypotheses are described as follows:

First Essay

The focal relationship of interest for the first essay is the influence of the urologists' medical school affiliation on the primary utilization of guideline discordant ADT on clinically localized prostate cancer patients. The implementation of the MMA (which is expected to moderate the focal relationship) will serve as the stimulus in eventually changing the physician practice behavior regarding the utilization of ADT. The specific conceptual model used for the first essay is shown in Figure 2.3. The following hypotheses are tested for the first essay.

First Essay Hypothesis 1

Urologists without major medical school affiliations are significantly more likely than those with major medical school affiliations to utilize guideline discordant ADT on prostate cancer patients.

First Essay Hypothesis 2

ADT reimbursement reductions following the passage of the MMA will weaken the positive relationship between urologists without major medical school affiliation and guideline discordant ADT use.

Second Essay

The focal relationship of interest for the second essay is the influence of the urologists' medical school affiliation on their diagnosed patient's subsequent radiation oncologist consultation. The specific conceptual model used for the second essay is shown in Figure 2.4. The following hypothesis is tested for the second essay.

Second Essay Hypothesis 1

Locoregional prostate cancer patients diagnosed by major medical school affiliated urologists (compared to patients diagnosed by urologists without major medical school affiliations) are significantly less likely to subsequently consult radiation oncologists.

Third Essay

The focal relationship of interest for the third essay is the influence of the radiation oncologists' medical school affiliation on the combined use of external beam radiation therapy (EBRT) and brachytherapy (BT) for clinically localized low-risk prostate cancer patients – a treatment regimen at variance with clinical practice guidelines. The specific conceptual model used for the third essay is shown in Figure 2.5. The following hypothesis is tested for the third essay.

Third Essay Hypothesis 1

Radiation oncologists with major medical school affiliations are significantly less likely than those without major medical school affiliations to utilize combined EBRT and BT on clinically localized low-risk prostate cancer patients.

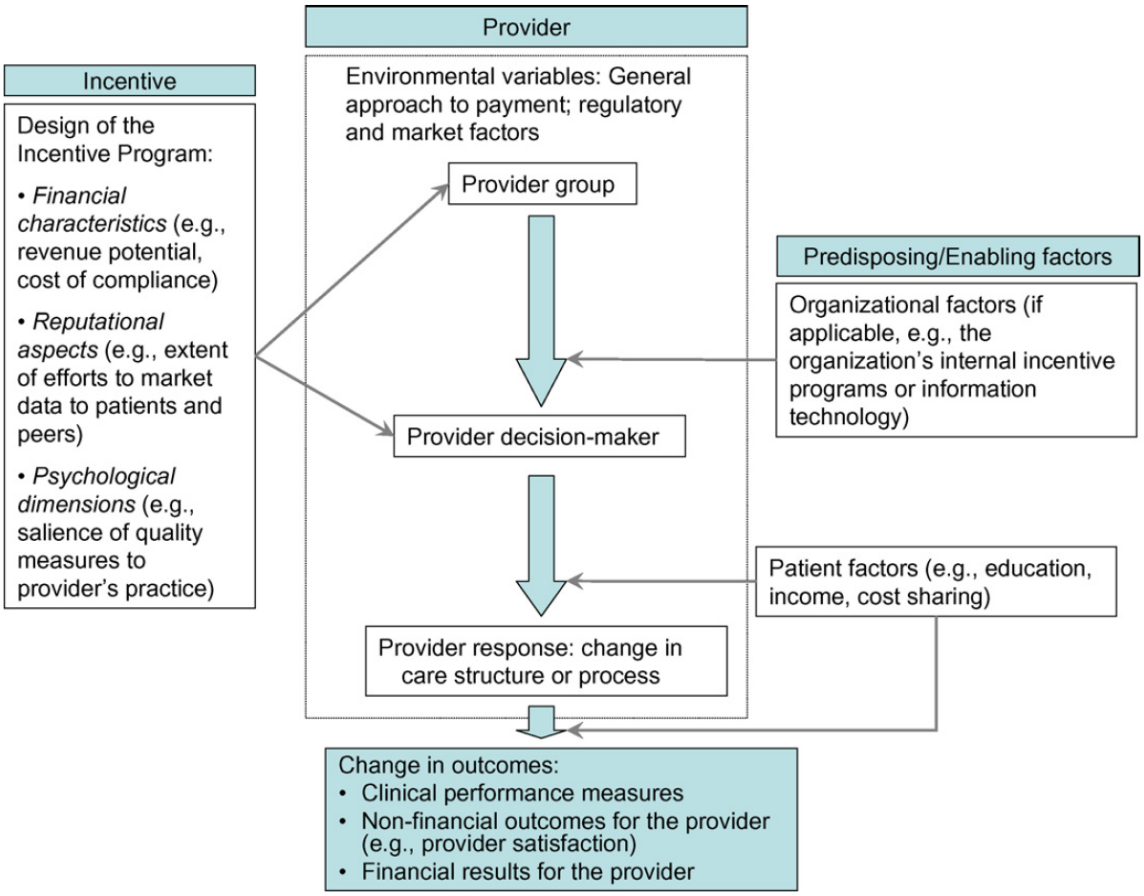


Figure 2.1 Conceptual model of the determinants of providers' responses to incentives developed by Frølich et al[4].

[4] Health Policy, 2007, 80(1), 179-193

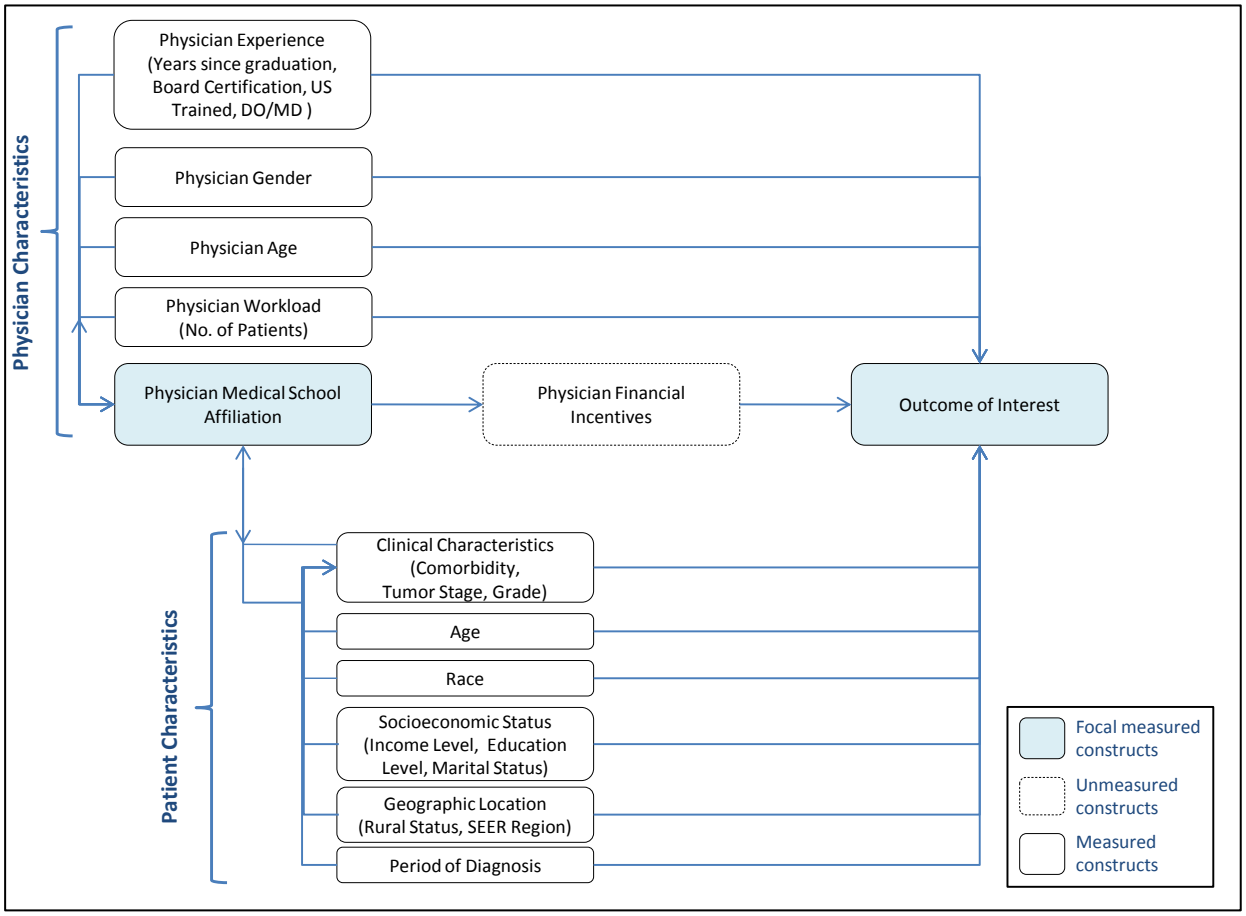


Figure 2.2 General conceptual model used for all three essays of this dissertation

Table 2.1 Description of Construct Measurements

Construct/ Measures	**Measures**		**Database Source**
	Description of Measures	Operationalization of Measures	
Dependent Variable			
First Essay: Medical Androgen Deprivation Therapy (ADT) Utilization	Measures ADT utilization identified from Medicare claims data.	Dichotomous: Medicare physician inpatient and outpatient claims will be used to identify utilization of ADT (Healthcare Common Procedure Coding System codes J9202, J9217, J9219, and J3315) within six months of prostate cancer diagnosis.	Medicare
Second Essay: Radiation Oncologist Consultation	Measures the referral pattern by the urologist to the radiation oncologist for the localized prostate cancer patient.	Dichotomous: If the patient had at least a physician claim within nine months post- diagnosis for localized prostate cancer and the attending physician self-designated specialty was radiation oncology, then the patient is defined as having consulted a radiation oncologist.	Medicare/ American Medical Association (AMA) Masterfile
Third Essay: Combined Use of External Beam Radiation Therapy and Brachytherapy	Measures combined radiation therapy utilization identified from Medicare claims.	Dichotomous: Medicare physician inpatient and outpatient claims will be used to identify utilization of combined external beam radiation therapy and brachytherapy (using Healthcare Common Procedure Coding System codes and International Classification of Diseases, Ninth Revision, Clinical Modification codes (ICD-9-CM)).	Medicare
Physician Medical School Affiliation (Key Independent Variable)			
Physician Medical School Affiliation	Indicates if the physician has Major, Minor, No Medical School affiliation or Non-institutional affiliation	Categorical: Physicians are categorized as having a major or no medical school affiliation if all their inpatient and outpatient Medicare claims submitted were from a hospital with a major or with no medical school affiliation, respectively. If physicians submitted claims only via non-institutional settings, they will be classified as having non-institutional affiliation. All other physicians will be categorized as having a mixed medical school affiliation.	SEER-Medicare Hospital file

Table 2.1 Description of Construct Measurements

Physician Financial Incentives (Mediator)			
Physician Financial Incentives	Not measured. Indirectly linked and full mediator of independent variable.		N/A
Moderator (Applies only to First Essay)			
Implementation of the Medicare Modernization Act of 2003 (MMA)	The MMA was instituted in December 2003 with a reduction in the reimbursement of ADT's average wholesale price (AWP) (from 2003's 95% to 80%–85%). Then in 2005, reimbursement decreased to effectively 40% to 50% of the 2003 ADT's AWP.	Categorical: Study period's year of analysis. (i.e. 2001 - 2007)	SEER
Patient Clinical and Sociodemographic Characteristics (Confounders)			
Comorbidity index	Based on an adaptation of the Charlson Comorbidity Index that was developed for use with Medicare physician claims data. Can range from 0 to 24, with higher scores indicating more coexisting conditions.	Categorical: Medicare inpatient and outpatient claims were searched for diagnostic codes of the ICD-9-CM. Each condition was weighted, and patients were assigned a score based on the Klabunde–Charlson index method. Index of interest:0, 1, 2, ≥3	Medicare
Clinical tumor stage	Describes the severity of cancer based on the extent of the original (primary) tumor and whether or not cancer has spread in the body	Categorical: SEER variables: Extent of Disease–Clinical Extension before 2004 and Collaborative Stage–Clinical Extension since 2004) (T1, T2, T3, T4)	SEER
Clinical lymph node metastasis stage (applies to second essay)	Describes the extent of lymph node metastasis	Categorical: N0 (No regional lymph node metastasis), N1 (Metastasis in regional node(s), NX (Regional lymph nodes not accessed) /Unknown	
Clinical tumor grade	Used to classify cancer cells in terms of how abnormal they look under a microscope and how quickly the tumor is likely to grow and spread	Categorical: Since 2003, tumor grade has been grouped as low (Gleason score: 2 to 4), intermediate (Gleason score: 5 to 6), or high (Gleason score: 7 to 10). Prior to 2003, intermediate (Gleason score: 5 to 7)	

Table 2.1 Description of Construct Measurements

PSA Level at Diagnosis (applies to second essay)	PSA Level (ng/mL) at Diagnosis	Categorical: 0.1-9.9, 10.0-20.0, >20.0, Unknown	
Race/Ethnicity	Race/Ethnicity	Categorical: Non-Hispanic White, Non-Hispanic Black, Hispanic, Non-Hispanic Asian/ Pacific Islander, Other/ Unknown	
Age at diagnosis	Age at diagnosis	Categorical: 66-69, 70-74, 75-79, 80-84, ≥85	
Rural Status	Distinguishes metropolitan counties by the population size of their metro area and nonmetropolitan counties by degree of urbanization and adjacency to a metro area or non-metro areas	Dichotomous: Rural versus Non-rural (Includes: Big Metro, Metro, Urban, Less Urban)	
SEER Region of Diagnosis	SEER Region patient diagnosed in	Categorical: Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Georgia (includes: Atlanta and Rural Georgia), Kentucky, New Jersey and California (includes: San Francisco, San Jose, Los Angeles, and Greater California). SEER data from Louisiana registry is excluded from analysis due to missing 2005 data following Hurricane Katrina	
Year of Diagnosis	Year of Diagnosis	Categorical: First Essay: 2001-2007 Second & Third Essay: 2004-2007	
Marital Status	Marital Status	Dichotomous: Married versus Not Married (Includes: Single, Separated, Divorced, Widowed, Unknown)	
Socio-economic Status (SES)	Population 2000 Census Tract-level Income	Quartiles: Median income levels will be assigned by census tract using US Census information from 2000	SEER/ Census
	Population 2000 Census Tract-level Education	Quartiles: % Adults with less than high school education will be assigned by census tract using US Census information from 2000	

Table 2.1 Description of Construct Measurements

Physician Characteristics (Confounders)			
Experience	Years since medical school graduation	Quartiles	AMA Masterfile
	Age	Quartiles	
Board Certification	Urology or Radiation Oncology board certification measured using information provided by the American Board of Medical Specialties	Dichotomous: Yes versus No	
U.S. Training	Country of Medical Training	Dichotomous: U.S. Trained versus Non-U.S. Trained	
Sex	Sex	Dichotomous: Female versus Male	
Degree Type	Type of Degree Holder	Dichotomous: Doctor of Medicine (MD) versus Doctor of Osteopathy (DO)	
Patient Panel Size	Defined as the number of patients with prostate cancer seen by physician during study period	Quartiles	Medicare

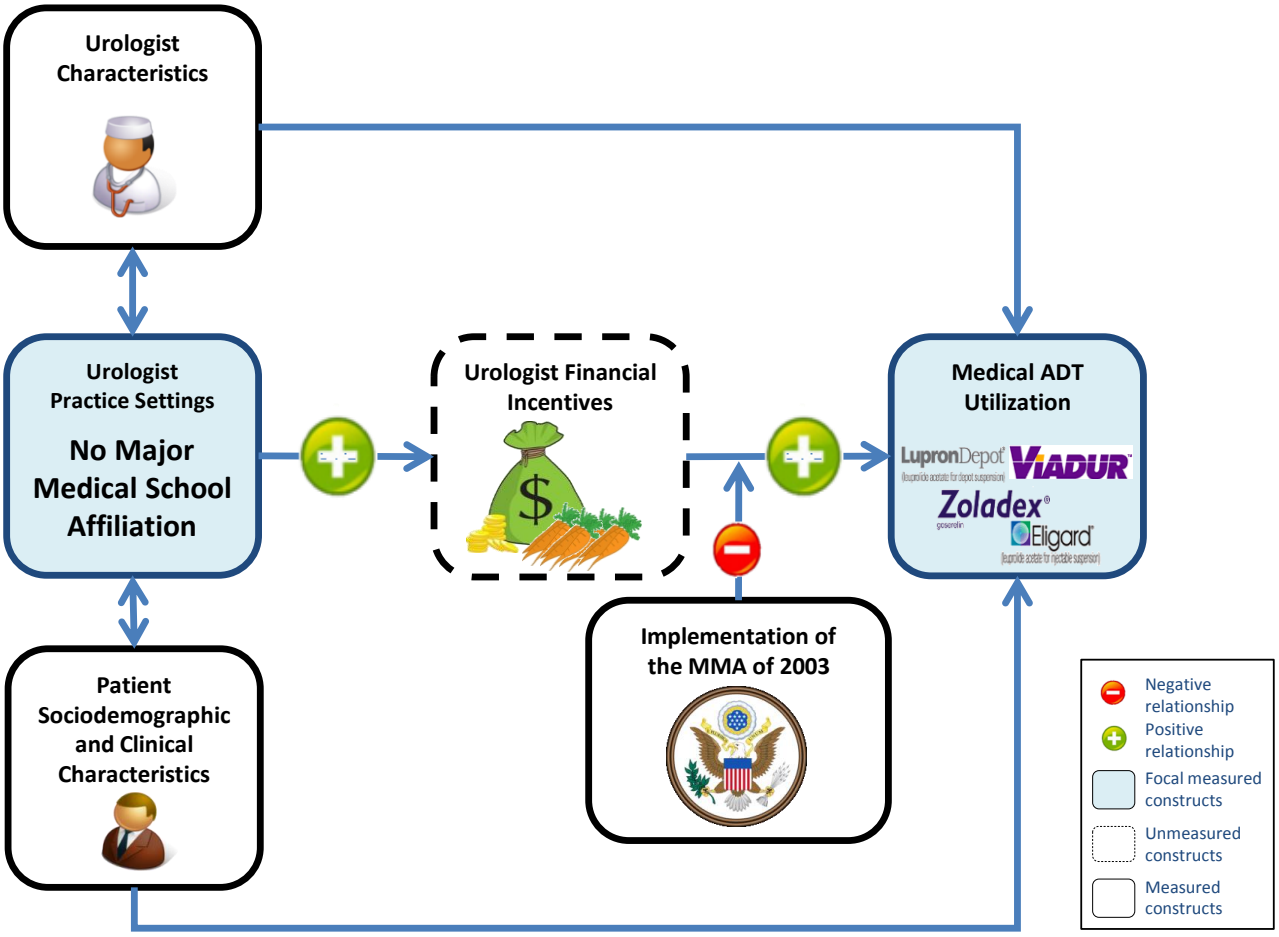


Figure 2.3 Specific conceptual model used for the first essay

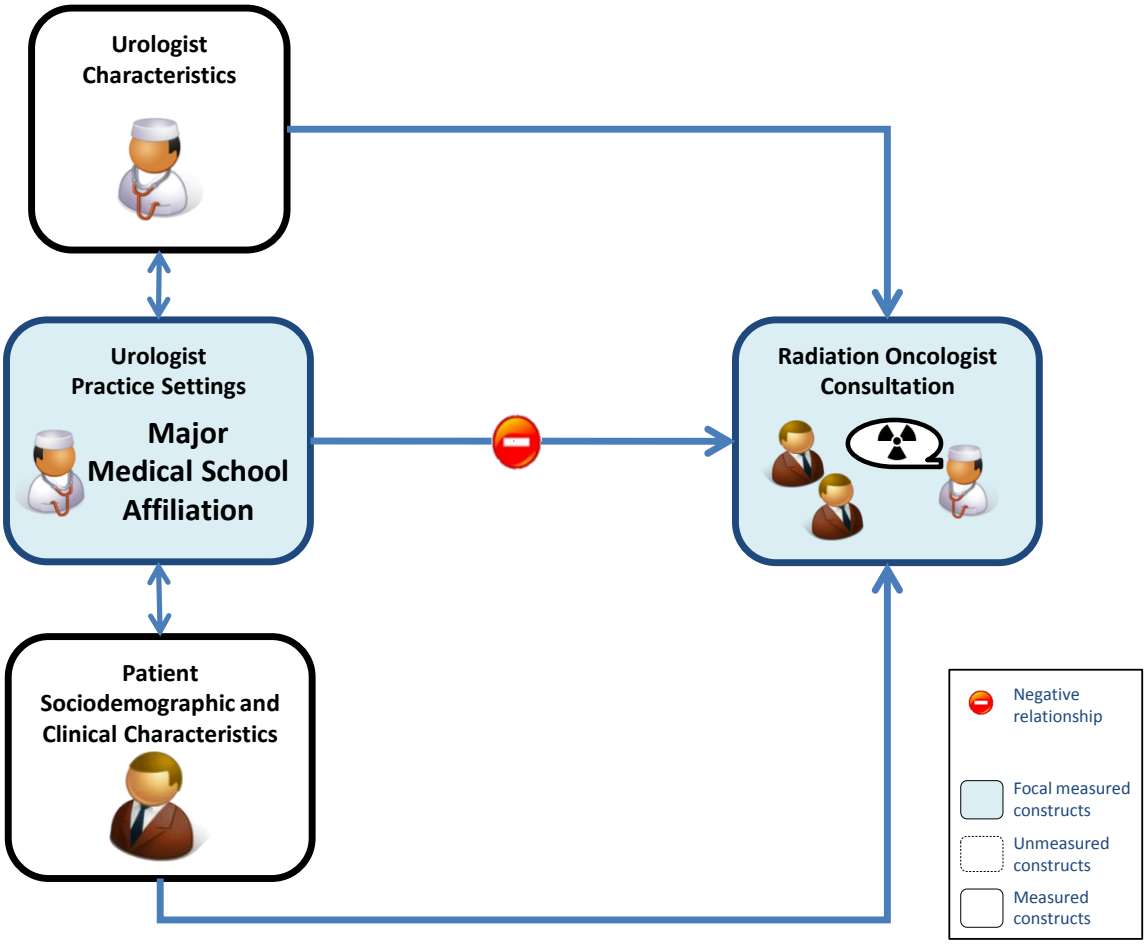


Figure 2.4 Specific conceptual model used for the second essay

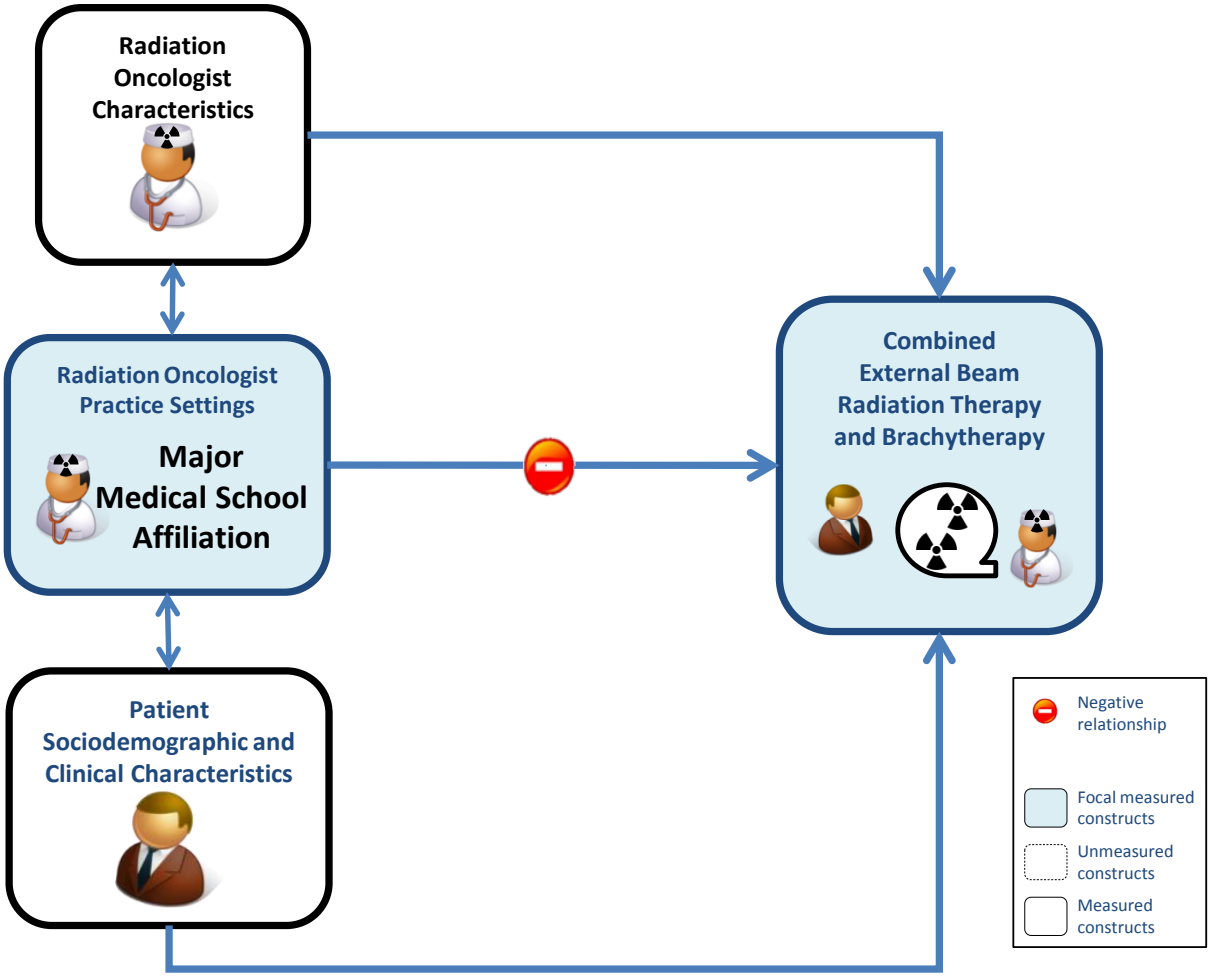


Figure 2.5 Specific conceptual model used for the third essay

CHAPTER 3 DATA SOURCES

Surveillance, Epidemiology and End Results – Medicare Database[1,2,3]

Surveillance, Epidemiology and End Results Program

The Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute collects cancer survival and incidence information from population-based cancer registries from selected geographic areas of the US. See Figure 3.1 for the different regions of the SEER program. The information collected about each incident cancer diagnosis includes patient sociodemographic characteristics, date of diagnosis, and cancer clinical characteristics (e.g. histology, grade, stage). The 16 registries used for all three essays of this dissertation encompass about 26% of the US population. The SEER data are broadly representative of the US population, although there are some differences. Demographically, the population of patients in the SEER database is more likely to be foreign born compared to the standard US 2000 population (18% vs 13%) (Figure 3.2). But note that there is variation between each of the SEER registries for some demographic factors. For example, there is significant variation between the SEER areas in the racial composition of persons 65 years and older. Some registries, such as Iowa and Utah, are almost exclusively White, while other registries – like San Francisco, Detroit, Hawaii, Atlanta and Los Angeles – have greater minority populations. Nonetheless, due to its large size and long follow-up, the SEER database is generally regarded as a sufficiently accurate representation of the US cancer population as a whole.

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[1] http://www.seer.cancer.gov/about/
[2] Oncology, 2009;23(3):288-95
[3] Medical Care, 2002;40(8 Suppl):IV-3-18.

The SEER data are considered highly valid. Every year, studies are conducted in the SEER areas to evaluate the quality and completeness of data reported. The SEER program's standard for the completeness of case ascertainment is 98%.

Medicare Data

Medicare is the primary health insurer for 97% of the US population 65 years and older. All Medicare beneficiaries receive Part A benefits, which cover inpatient care (including hospitals, skilled nursing facilities, home health, and hospice care). About 95% of Medicare beneficiaries also subscribe to Medicare Part B, which covers services like physician services, outpatient care, durable medical equipment.

SEER-Medicare Linkage

SEER data are linked with Medicare claims based on an algorithm involving a match of social security number, name, sex and date of birth. For each of the linkages, among persons in the SEER database aged 65 or older, about 93% were found to be enrolled in Medicare. There is a lag of approximately two years in the reporting of cases to the SEER program. SEER-Medicare linkages are updated every 3 years.

Data files in the Surveillance, Epidemiology and End Results – Medicare Database

The SEER-Medicare data are stored in a number of separate files. The Patient Entitlement and Diagnosis Summary File (PEDSF) contains sociodemographic variables as well as clinical information for up to 10 diagnosed cancer cases. Each Medicare file varies in the claim data elements included and the type of procedure and diagnostic codes used, either International Classification of Diseases Ninth Edition (ICD-9) codes for procedures and diagnoses or Health Care Financing Administration Common Procedure Coding System (HCPCS) codes for procedures. HCPCS are the American

Medical Association (AMA)'s Common Procedure Terminology fourth edition codes (CPT-4), with additional codes used exclusively by Centers for Medicare & Medicaid Services (CMS). In general, all Medicare claims contain information about charges, reimbursement, and an identification number for the provider (e.g. hospital) and/or physician. In addition, every Medicare file contains a unique anonymized identifier number assigned to each patient by the SEER registries. This patient identifier number allows for the linkage of information across multiple SEER-Medicare files.

Data Limitations

Some health care services are not captured in Medicare Claims. Services not covered include routine physical examinations, oral prescription drugs (prior to 2006), long-term care, and until recently many types of cancer screening. Similarly, there are no Medicare claims in cases where the beneficiary receives services covered by Medicare but not billed to Medicare. This may include care received by a beneficiary who is still working and is covered by an employer's health insurance where Medicare is a secondary payer, or services provided to a Medicare beneficiary by a Veterans Health Administration facility.

SEER-Medicare is generally good for studying beneficiaries covered via Medicare's traditional Fee-For-Service (FFS) program. However, Health Maintenance Organizations have historically not been legally required by Centers for Medicare and Medicaid (CMS) to submit all claims for services received by their enrollees. The lack of complete claims data for Health Maintenance Organization (HMO) enrollees is a significant limitation of the Medicare database. As or 2003, 89% of Medicare beneficiaries are covered under the traditional FFS program and that figure has dropped to 76% by 2010. There is also wide geographic variation across the US in HMO penetration rates. In addition, Medicare

beneficiaries are also allowed to switch their plans (e.g. from HMO to FFS). Such freedom of movement between types of plans increases the chance that some claims data will be missing on those patients who are covered under a HMO plan during some portion of the study's observation period. HMO enrollees tend to be younger and healthier than those in FFS, resulting in a biased loss of information in the claims data.

American Medical Association Physician Masterfile[4,5]

The AMA Physician Masterfile contains information of all physicians in the US, Puerto Rico, the Virgin Islands, and certain Pacific Islands regardless of membership in the AMA. The information is collected from primary sources such as medical schools, residency training programs, state licensing agencies, Drug Enforcement Agency, the Educational Commission for Foreign Medical Graduates, obituaries, death certificates, medical societies, state medical boards, and the American Board of Medical Specialties (ABMS). The AMA also conducts an annual survey (electronically and via mail) of approximately one third of the roughly 800,000 physicians listed within the AMA Physician Masterfile (40% response rate) regarding their latest practice. The AMA Physician Masterfile can be linked to the SEER-Medicare database via the Unique Physician Identification Number (UPIN). Such a linkage has been found to be very consistent across SEER registries and patients' geographic state of residence. See Figure 3.3 for the location of key variables across the different SEER-Medicare database and the AMA Physician Masterfile.

[4] Medical Care 2002;40(8 Suppl):IV-82-95.
[5] http://www.ama-assn.org/ama/pub/about-ama/physician-data-resources/physician-masterfile.page

Data Limitations

Variables obtained from sources other than the physician survey are fairly complete and unlikely to change over time. However, variables obtained through the physician survey are subject to the limitations associated with its low response rate. If a physician has never responded to the survey, much of the practice characteristics data will be missing. If a physician responds to the survey initially but does not respond to updates, changes in practice characteristics may not be reflected in the AMA Physician Masterfile.

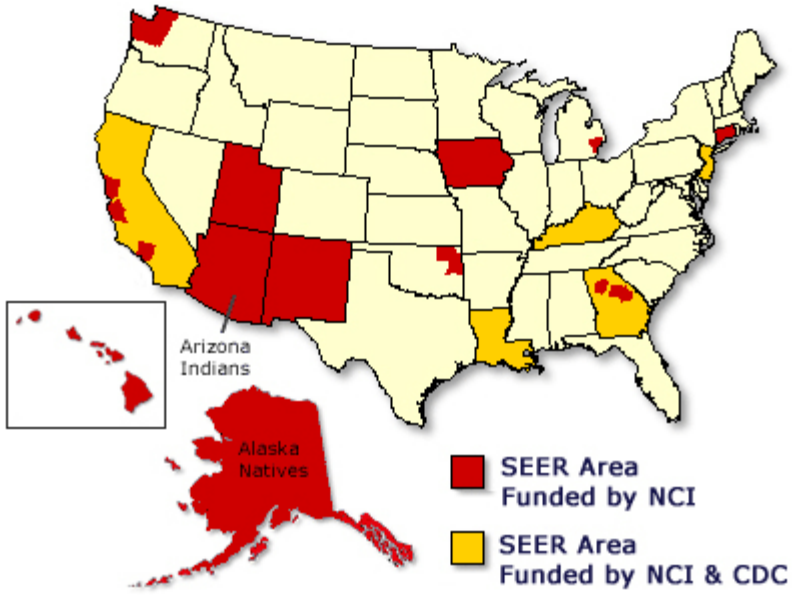
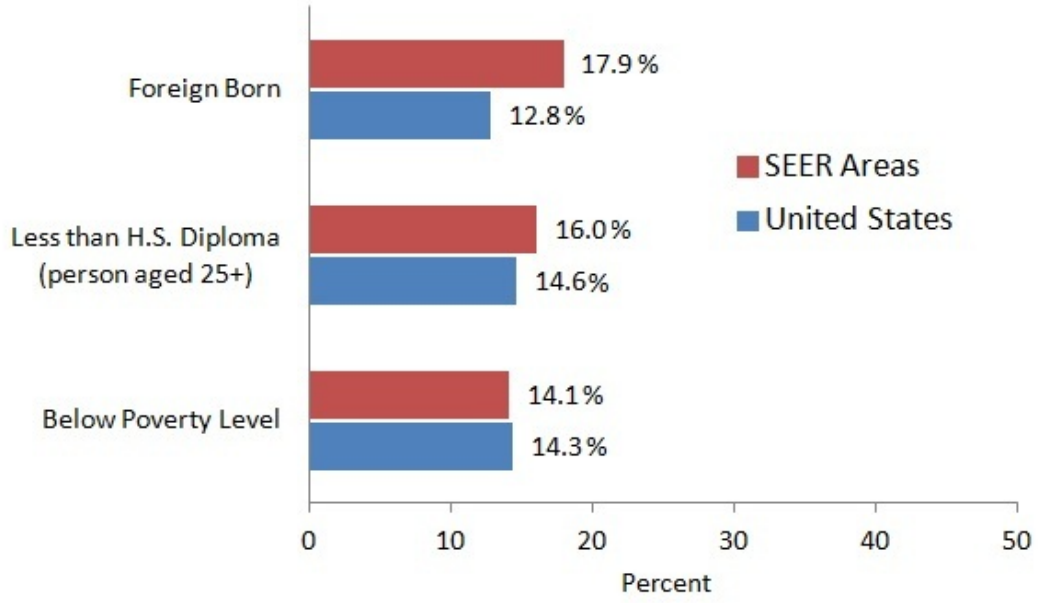


Figure 3.1 Regions of SEER program funded by the National Cancer Institute (NCI) and the Centers for Disease Control and Prevention (CDC)[6]

[6] http://www.seer.cancer.gov/registries/



* The data source for these statistics is the U.S. Census Bureau, 2007-2011 American Community Survey. SEER areas included in this figure are the States of Connecticut, Hawaii, Iowa, Kentucky, Louisiana, New Jersey, New Mexico, Utah; multi-country areas of Atlanta, rural Georgia, remaining counties of Georgia, Detroit, San Francisco-Oakland, Seattle-Puget Sound, San Jose-Monterey, Los Angeles county, remaining counties of California; and American Indians/Alaska Natives in Arizona, Alaska and Cherokee Nation.

Figure 3.2 Characteristics of the SEER population compared with the total United States population[7]

[7] http://www.seer.cancer.gov/registries/characteristics.html

SEER - Medicare					AMA	
PEDSF	**OUTSAF**	**NCH**	**MEDPAR**	**HOSP**	**AMAPM**	**ABMS**
Patient ID	Patient ID	Patient ID	Patient ID			
Diagnosis Date	Claim From Date	Claim From Date	Admission Date			
	Claim Through Date	Claim Through Date	Discharge Date			
	Physician ID	Physician ID			Physician ID	Physician ID
		Physician Specialty			Physician Specialty	Physician Specialty
	Provider ID	Place of Service	Provider ID	Provider ID		
				Medical School Affiliation		

Figure 3.3. Location of key variables across different files of the Surveillance, Epidemiology and End Results (SEER) – Medicare database and American Medical Association (AMA) Physician Masterfile; PEDSF, Patient Entitlement and Diagnosis Summary File; OUTSAF, Outpatient Standard Analytical File; NCH, National Claims History records; MEDPAR, Medicare Provider Analysis and Review file; HOSP, Hospital File; AMAPM, American Medical Association Physician Masterfile; ABMS, American Board of Medical Specialties; ID, Identifier

CHAPTER 4 ANALYTIC STRATEGY

X^2 Test of Homogeneity[1]

For all three essays of this dissertation, X^2 tests of homogeneity are used to examine whether two populations have the same proportion of observations with a common categorical characteristic. X^2 tests are used to determine whether frequency counts are distributed identically across different populations. At any specified level of the categorical variable, the null hypothesis states that each population has the same proportion of observations.

Expected frequency counts

The expected frequency counts are computed separately for each population at each level of the categorical variable, according to the following formula:

$$E_{r,c} = (n_r * n_c) / n$$

where $E_{r,c}$ is the expected frequency count for population r at level c of the categorical variable, n_r is the total number of observations from population r, n_c is the total number of observations at treatment level c, and n is the total sample size.

Test statistic

The test statistic is a chi-square random variable (X^2) defined by the following equation:

$$X^2 = \Sigma [(O_{r,c} - E_{r,c})^2 / E_{r,c}]$$

where $O_{r,c}$ is the observed frequency count in population r for level c of the categorical variable, and $E_{r,c}$ is the expected frequency count in population r for level c of the categorical variable.

[1] http://stattrek.com/chi-square-test/homogeneity.aspx

Hierarchical Generalized Linear Mixed Models[2]

Generalized Linear Mixed Models (GLMM) are extensions of Generalized Linear Models (GLM) by the inclusion of random effects. A random effect is a random variable that is included in a regression model to account for the natural heterogeneity among subjects on the prediction of an outcome variable of interest. Random effects are associated with the sampling procedure, whereas fixed effects affect the population means. In GLMMs, random effects contribute only to the covariance structure of the data. The presence of random effects, however, often introduces correlations between subjects, and GLMMs allow for the adjustment for covariance structure of the data.

The fixed effects of GLMs are based on the likelihood function of the data. In the GLMM, estimation and inference are also based on the marginal log-likelihood or residual log-likelihood function of the data. The marginal distribution is obtained by integrating the joint distribution of data and random effects over the random effects. In cases where the random effects are normally distributed and the outcome is not normally distributed, the marginal distribution can be estimated based on an approximated model. This is the pseudo-likelihood approach taken by SAS's GLIMMIX procedure.

In all three essays of this dissertation, the outcomes of the patients tend to be clustered within the physicians that treated them (Figure 4.1). Hierarchical GLMMs were used to account for the clustering of outcomes among patients (Level 1) treated by the same physician (Level 2).

Hierarchical GLMM will allow for violation of the assumption that the error terms are independently and identically distributed (as assumed for standard linear models). Estimations derived from hierarchical GLMM will thus lead to a lower type 1 error rate;

[2] SAS for Mixed Models, 2nd Edition, 2006

standard errors of the parameters used in non-GLMMs are smaller in cases where clustering is present, even if estimates of the regression parameters are similar to those of GLMMs.

Covariance Structure

The covariance structure used in all three essays of this dissertation is shown in Figure 4.2. There are as many rows (and columns) as there are level 1 individuals (i.e. patients). In Figure 4.2, the covariance structure for the first 6 patients is shown. The first three level 1 individuals (i.e. Patient 1, 2, 3) are treated by cluster 1 (i.e. Physician A) and the subsequent three level 1 individuals (i.e. Patient 4, 5, 6) are treated by cluster 2 (i.e. Physician B). The total residual variance for each patient in the model is the sum of the within-physician residual (σ^2) and the between physician residual (τ_{00}). The covariance between any two or more patients who are treated by the same physician is accounted for by τ_{00}. The residual covariance between patients treated by two different physicians is assumed to be 0.

Model Building Approach

In a hierarchical GLMM, the hierarchical structure appears in the linear regression equation of the GLMM. With the subscripts $_i$ and $_j$ identifying the patient and the physician, respectively, a two-level null model (Model 1) for proportions is written as follows:

$Y_{ij} \mid \pi_{ij} \sim B(m_{ij}, n_{ij})$

$\eta_{ij} = \log [\pi_{ij} /(1- \pi_{ij})] = \text{Logit } P(Y_{ij}) = \beta_{0j}$ Patient Level (Level 1)

$\beta_{0j} = \gamma_{00} + u_{0j}, \quad u_{0j} \sim N(0, \tau_{00})$ Physician Level (Level 2)

$\eta_{ij} = \gamma_{00} + u_{0j}$ Model 1 (Mixed Model)

The dichotomous outcome Y_{ij} variable is a proportion π_{ij}. The probability distribution for π_{ij} is binomial (m_{ij}, n_{ij}) with mean $m_{ij.}$ The logit link function was used and conditional on the predictor variables, π_{ij}, was assumed to have a binomial error distribution with expected mean m_{ij} and number of trials n_{ij}. It is assumed that the logit transformation of the outcome variable has a linear relationship with the predictor variables. Since the error distribution is assumed to be binomial, the variance is a function of the population proportion π_{ij}: $\sigma^2 = \pi_{ij} / (1- \pi_{ij})$. η_{ij} is log of the odds of patient i treated by physician j.

γ_{00} is the unadjusted grand mean across all physicians of the log odds of the outcome of patient being treated by a specific physician. u_{0j} is the normally distributed random effect for the j^{th} physician. Patient level random errors are assumed to be independent from u_{0j}. τ_{00} is the variance between physicians in the physician-average log-odds of the level 1 outcome.

The null model (model 1) without explanatory variables was initially used to confirm that η_{ij} does indeed vary by physician. It provides information about the variability of outcome at both patient and physician levels.

Significant variance at the individual level may result from sampling. The differences between patients may possibly lead to significant variance at physician level. To reduce the competing explanation (for why physician-level matters), individual patient level characteristics were subsequently modeled (Model 2).

$\eta_{ij} = \beta_{0j} + \Sigma \beta_{jk} x_{ijk}$ Patient Level (Level 1)

$\beta_{0j} = \gamma_{00} + u_{0j}, \quad u_{0j} \sim N(0, \tau_{00})$ Physician Level (Level 2)

$\beta_{jk} = \gamma_{jk}$

$\eta_{ij} = \gamma_{00} + \Sigma\, \gamma_{jk} x_{ijk} + u_{0j}$ Model 2 (Mixed Model)

γ_{00} is the adjusted grand mean across all physicians of the log odds of patients treated by a specific physician. x_{ijk} is the characteristic k (e.g. age, race/ethnicity, socioeconomic status, geographic location, clinical characteristics) of the i^{th} patient treated by the j^{th} physician. γ_{jk} estimates the impact of that characteristic.

If the variance at the physician level is still significant after accounting for patient factors, this provides evidence that factors at the physician level play a role in understanding outcome variation across physicians. Following from this, the final step is to include the possible predictors at the physician level into the model (Model 3).

$\eta_{ij} = \beta_{0j} + \Sigma\, \beta_{jk} x_{ijk}$ Patient Level (Level 1)

$\beta_{0j} = \gamma_{00} + \Sigma\, \gamma_{0l} w_{jl} + u_{0j}, \;\; u_{0j} \sim N(0, \tau_{00})$ Physician Level (Level 2)

$\beta_{jk} = \gamma_{jk}$

$\eta_{ij} = \gamma_{00} + \Sigma\, \gamma_{0l} w_{jl} + \Sigma\, \gamma_{jk} x_{ijk} + u_{0j}$ Model 3 (Mixed Model)

w_{jl} is characteristic l (i.e. experience, gender, age, workload) of the j^{th} physician. γ_{0l} is the impact of physician characteristic l.

Intraclass Correlation Coefficient

For the logit model, the underlying logistic distribution can be described by:

$$f(x) = \frac{\exp(x)}{[1+\exp(x)]^2}$$

with cumulative distribution function (CDF):

$$\int_{-Y}^{\infty} f(x)dx = [1+\exp(-Y)]^{-1}$$

The right hand side of the CDF is simply the logit link function model with Y as the linear component incorporating level 2 variation. The variance for the standard logistic distribution is $\pi^2/3 = 3.29$ so this is taken to be the level 1 (i.e. η_{ij}) variance.

Hierarchical GLMMs allow for the simultaneous estimation of the effects of higher level (i.e. physician-level) and Level 1 (i.e. patient-level) factors and partitioning of the outcome variance between patient and physician levels. This allows for the calculation of the Intraclass Correlation Coefficient (ICC). The ICC represents the degree of correlation between individuals within a group.

$$\text{ICC} = = \frac{\tau_{00}}{\tau_{00}+\frac{\pi^2}{3}} = \frac{\tau_{00}}{\tau_{00}+3.29}$$

Here, τ_{00} represents variance due to between-physician differences and 3.29 represents the variance due to within physician differences (i.e. between patient differences).

Collinearity Diagnostics[3]

Collinearity measures the extent to which one or more of independent variables in the chosen model can be predicted from another independent variable in the model. If there is a high correlation among some of the predictors, the fitted model may yield unreliable regression coefficients for some predictors.

A SAS macro developed by Kleinbaum, Delaney, et al. was used to test for multicollinearity for all three essays of this dissertation. Collinearity would be an issue in a model if the largest of the condition indices is considered large (i.e. >30) and at least

[3] Applied Regression and Other Multivariable Methods, 4th Edition, Chapter 14, 2008

two of the variance decomposition proportions are large (i.e. >0.5). In the analyses for each of the three essays, the condition indices were found to be < 30 for the final fitted models. For exact mathematical details regarding condition indices and variance decomposition proportions, see *Applied Regression and Other Multivariable Methods*, 4th Edition, Chapter 14 by Kleinbaum et al.

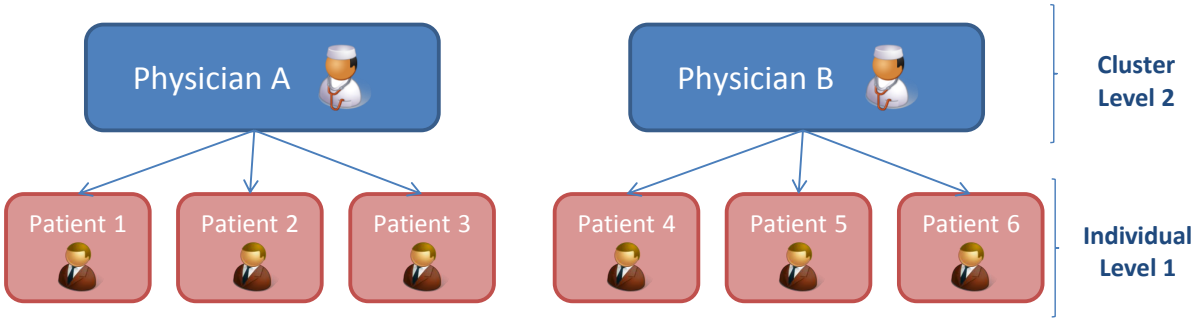


Figure 4.1 Patients clustered within individual physicians

$$\begin{bmatrix} \sigma^2+\tau_{00} & \tau_{00} & \tau_{00} & 0 & 0 & 0 & \cdots \\ \tau_{00} & \sigma^2+\tau_{00} & \tau_{00} & 0 & 0 & 0 & \\ \tau_{00} & \tau_{00} & \sigma^2+\tau_{00} & 0 & 0 & 0 & \\ 0 & 0 & 0 & \sigma^2+\tau_{00} & \tau_{00} & \tau_{00} & \\ 0 & 0 & 0 & \tau_{00} & \sigma^2+\tau_{00} & \tau_{00} & \\ 0 & 0 & 0 & \tau_{00} & \tau_{00} & \sigma^2+\tau_{00} & \end{bmatrix}$$

Figure 4.2 Covariance structure for a 2-level model with random intercepts

CHAPTER 5 FIRST ESSAY — REIMBURSEMENT POLICY AND USE OF MEDICAL ANDROGEN DEPRIVATION THERAPY FOR CLINICALLY LOCALIZED PROSTATE CANCER

Introduction

The importance of androgen deprivation therapy (ADT) for metastatic prostate cancer has been established for more than 70 years[1,2]. During the early 1990s to the early 2000s, ADT in the form of luteinizing hormone-releasing hormone (LHRH) agonists[3] (an injectable form of ADT), has increased steadily among prostate cancer patients across all stages and grades[4,5].

Part of the growth may be due to extended indications for ADT; ADT has been recommended by clinical guidelines[6-13] for the palliation of systematic metastases and adjuvant therapy in radiation and surgery for prostate cancer. However, serious adverse effects and deterioration in quality of life associated with ADT[14-20] resulted in guidelines not recommending primary ADT for clinically localized, low-intermediate risk prostate cancer[6-11,13,21]. Previous research suggests that growth in ADT use may also be the result of Medicare reimbursement policy that made prescription of LHRH agonists profitable for urologists[22-25]. By 2003, LHRH agonists' Medicare Part B expenditures peaked at USD 1.23 billion[23]. The U.S. federal government, as part of the 2003 Medicare Modernization Act[26] (MMA), drastically reduced the LHRH agonists Medicare reimbursement rate; Medicare payment rate for leuprolide acetate (i.e. the most common form of LHRH agonists) fell by almost 50%[27] in 2005. These Medicare reimbursement changes consequently affected the practice patterns[22-25,27] and incomes[28] of urologists depending on their practice setting.

Studies have shown that variation in the primary treatment of prostate cancer can be influenced by the physicians' practice setting[29]. Urologists play an important role in whether patients receive ADT[30]; clinically localized prostate cancer patients treated by non-academically affiliated urologists are significantly more likely to receive primary ADT[31]. To my knowledge, no research has evaluated the role of the urologists and their medical school affiliation in the receipt of primary ADT for clinically localized prostate cancer before and after the passage of the MMA.

In this study, I investigated the association of urologist characteristics, including their medical school affiliation on the receipt of primary ADT among clinically localized, clinical stage T1-T2, low-intermediate grade prostate cancer patients-a treatment regimen at variance with clinical guidelines. I hypothesized that major medical school affiliated urologists would less likely prescribe guideline discordant primary ADT before and after the passage of the MMA.

Methods

Data Sources

The Surveillance, Epidemiology and End Results (SEER)-Medicare database that links cancer registry information in selected U.S. geographic areas with health care claims of Medicare beneficiaries[32] is used to create my analytical cohort using the criteria given in Figure 5.1. During the study period, incident cancer cases are available from 16 cancer registries from 2001-2007. Louisiana SEER registry data are removed from this study due to missing 2005 information following Hurricane Katrina. Data from metropolitan Atlanta and Rural Georgia SEER registries are hereinafter classified as Georgia.

Characteristics of physicians who treated SEER-Medicare patients are extracted from the American Medical Association (AMA) Physician Masterfile.

Institutional review board approval was obtained from Morehouse School of Medicine and Emory University.

Patient Characteristics

Patient characteristics used in the study are found in Table 5.1. To access the prevalence of comorbid disease, a modified Charlson comorbidity index from Medicare Part A and Part B claims[34,35] was calculated. Specifically, International Classification of Diseases, Ninth Revision, Clinical Modification codes consistent with comorbidities of interest are examined from one year before to one month after cancer diagnosis. Year of diagnosis, race, ethnicity, age, marital status, rural status, SEER region of residence at time of diagnosis, clinical stage (T1-T2) and tumor grade (low, Gleason grade 2-4; intermediate, years of diagnosis 2001-2002: Gleason grade 5-7, years of diagnosis 2003-2007, Gleason grade 5-6) were extracted from SEER files. The differences in

intermediate grade definition across the different years of diagnosis are due to changes in SEER coding[36]. Education and income levels are based on the 2000 U.S. Census tract data; the pre-specified categories correspond to quartiles.

Patients who received radiation therapy or radical prostatectomy (previously defined[24]) are removed from the study cohort. By focusing on a more homogenous population in terms of treatment selection, I avoided the uncertainty that can be caused by changes in evidence supporting adjuvant ADT (i.e. ADT combined with radiation[37,38] or radical prostatectomy[39,40]). Additionally, patients who received bilateral orchiectomy are removed as this study focused solely on medical ADT which was subjected to the MMA reimbursement reductions.

To assign a principal urologist to each patient, criteria are adopted from Shahinian et al.[31]. Patients who did not see at least one urologist in the year after diagnosis on at least 2 separate days were excluded. If a patient saw two or more urologists, he was assigned to the urologist who saw him for at least 75% of his urologist visits in the year after diagnosis. If no single urologist accounted for at least 75% of all urologist visits associated with that patient, he was excluded.

Urologist Characteristics

Urologists are identified using either the Health Care Financing Administration specialty codes in Medicare claims, urology board certification identified through the ABMS information or the physician specialty (primary/secondary) information within the AMA Physician Masterfile. Other urologist characteristics obtained from the AMA Physician Masterfile included, age, gender, years after medical school graduation, location of training (U.S. or otherwise), type of degree [Doctor of Medicine (MD) or Doctor of Osteopathy (DO)] and urology board certification (Table 5.1). Urologist patient volume is

defined as the number of unique prostate cancer patients each urologist saw during the study period. The pre-specified categories for urologist patient volume, age, and years after medical school graduation correspond to quartiles.

Urologist Medical School Affiliation

Figure 3.3 in Chapter 3 summarizes the source files for key variables used to categorize urologist's medical school affiliation. Such affiliations are derived from the SEER-Medicare Hospital (HOSP) file and adapted from previously described methods[31,41]. Urologists are categorized as having a major medical school affiliation if all their inpatient [in Medicare Provider Analysis and Review (MEDPAR) file] and institutional outpatient [in Medicare Outpatient Statistical Analytical File (OUTSAF)] claims during the study period are submitted from hospitals with a major medical school affiliation (defined in HOSP file). Conversely, urologists are categorized as having had no medical school affiliation if all of their inpatient and institutional outpatient claims are from hospitals without medical school affiliation. Since claims from the MEDPAR file do not contain Unique Physician Identifier Numbers (UPIN), MEDPAR claims are assigned UPINs associated with National Claims History (NCH) file (consisting of mostly non-institutional physician/supplier claims) claims if 1) the patient associated with both types of claims matched, 2) the NCH place of service was institutional[42] and 3) the NCH claims dates fell between the MEDPAR admission and discharge dates. Urologists whose claims could be found only in the NCH file and whose claims could not be matched with the MEDPAR file (as previously described) are categorized as having a non-institutional affiliation. All other urologists are categorized as having a mixed medical school affiliation.

Measurement of Treatment and Outcomes

The primary outcome is the receipt of primary ADT. ADT is defined as the receipt of at least one dose of LHRH agonist[24] in the first six months after clinical stage T1-T2, low-intermediate grade prostate cancer diagnosis. Therefore, this study is limited to investigating if ADT is used as an initial therapy-a treatment regimen at variance with clinical guidelines[6-13,21].

Statistical Analyses

Differences in the proportion of patients receiving ADT across urologist and patient characteristics are evaluated using χ^2 tests. The effect of urologist and patient characteristics on ADT utilization is evaluated using logistic hierarchical generalized linear mixed models[43] (GLMM) and estimated using the restricted pseudo-likelihood methodology[43-45]. Hierarchical GLMM accounted for the clustering of ADT among patients treated by the same urologist. The unit of analysis is the patient. The urologist associated with each patient is used as the clustering variable. Univariate and adjusted multivariate odds ratio (ORs) and 95% confidence intervals (CIs) for the receipt of ADT are calculated for each variable (Table 5.2).

The mean predicted probability of ADT use, stratified by medical school affiliation of the patient's urologist, is estimated from the final fitted model (Figure 5.2). Two sets of linear regressions are fitted (Figure 5.3) across two periods of interest (pre-MMA: 2001-2003, post-MMA: 2003-2007). Since the MMA was passed in December 2003, 2003 is included in both regression sets. Additionally, linear regressions are fitted for each medical school affiliation category. The significance of the overall trend and the differences in slopes between periods of diagnosis by medical school affiliations are evaluated using t-tests. All statistical testing is two-sided and performed at the 5% significance level, and analyses are performed using SAS version 9.3 (SAS Institute, Cary, NC).

Results

I identified 14,911 men in the SEER-Medicare database who were diagnosed with prostate cancer from 2001-2007 and who met the eligibility criteria (Figure 5.1). 1,943 urologists treated these patients. These urologists are predominantly male (97.4%), board certified (93.3%), had a patient volume of less than 38 (52.4%) throughout the study period, U.S. trained (83.9%) and are MDs (97.6%) (Table 5.3).

Table 5.1 compares the percentages of patients who received ADT by their sociodemographic, clinical and urologist characteristics. Overall, 5,452 (36.6%) patients received ADT that is at variance with guidelines. ADT was more commonly administered to patients who are older, have a minority race/ethnicity, unmarried, residing in New Jersey and/or in census tracts with lower educational and/or median incomes levels, have intermediate tumor grade, have clinical stage T2, and diagnosed in the early 2000s. The principal urologists associated with patients who received ADT were likely to have more than 16 years of experience after medical school graduation, a patient volume of more than 82, no medical school affiliation, 42 years or older, non-U.S. trained and non-board certified.

Using the unadjusted hierarchical GLMM, I investigated the factors associated with ADT (Table 5.2) while controlling for the clustering of patients treated by the same urologist. As the unadjusted odds ratios show, ADT is more commonly and significantly associated with patients who are older, non-Hispanic Black race/ethnicity, residing in New Jersey as compared to Georgia, residing in census tracts with lower education and/or median income levels, clinical stage T2, intermediate grade tumor and diagnosed in early 2000s. Likewise, principal urologists characteristics more commonly and significantly associated with ADT use were the lack of urology board certification, non-US trained, 17 or more

years of experience after medical school graduation and having non-major medical school affiliation.

After adjusting for patient and urologist characteristics, ADT was significantly associated with the non-Hispanic Asian/Pacific Islander race/ethnicity. Urologists with non-major medical school affiliations and/or without US medical training remained significantly associated with ADT. Patients treated by urologists without a medical school affiliation are significantly associated with ADT (odds ratio [OR], 2.35; 95% confidence interval [95% CI], 1.77-3.12, $p<0.0001$).

Both Tables 5.1 and 5.2 show that the respective proportion and odds of ADT are the highest in 2001. The mean predicted probabilities show a downward trend in ADT for patients across all categories of urologists' medical school affiliation for the different years of diagnosis (Figure 5.2). Probability of ADT is higher for patients who were treated by urologists without medical school affiliation (2001: 47.5%, 2007: 23.8%) compared to patients treated by major medical school affiliated urologists (2001: 38.7%, 2007: 16.3%).

Overall, there was a significant ($t=-2.79$, $p=0.005$) reduction in ADT during the study period. Pre-MMA (i.e. 2001-2003), the fitted linear regression slope of ADT for patients treated by major medical school affiliated urologists is significantly steeper ($t=2.39$, $p=0.02$) compared to the slope for those treated by urologists without medical school affiliations. But post-MMA (i.e. 2003-2007), the slope of ADT for patients treated by urologists without medical school affiliation is steeper ($t=-0.38$, $p=0.70$) compared to the slope for those treated by major medical school affiliated urologists (Figure 5.3).

Discussion

Even after four years post-MMA, 22% of prostate cancer patients who met the inclusion criteria still received guideline discordant primary ADT. Although patient factors affected ADT use patterns, urologists' characteristics and their medical school affiliation in particular, are significantly associated with guideline discordant ADT throughout the study period.

To my knowledge, this is the first study using Medicare inpatient, outpatient and non-institutional claims to categorize urologists' medical school affiliations. Similarly, this is the first study that compared the influence of urologists' medical school affiliation on ADT before and after the passage of the MMA. Overall, the post-MMA period is associated with a steeper drop in ADT by urologists without medical school affiliation vis-à-vis patients treated by major medical school affiliated urologists. My findings suggest that the MMA may have led to increased ADT guideline compliance by non-medical school affiliated urologists toward levels observed for major medical school affiliated urologists. My study also showed that the drop in ADT use may have started about 3 years before MMA; although rates of decrease differed before and after the passage of the MMA and were dependent on urologists' medical school affiliation. Other significant associations found between ADT and other patient and urologist characteristics complement previous findings[22,24,31].

Multiple factors may have influenced trends observed across the different categories of urologists' medical school affiliation. Research has shown that payment mechanisms influence physicians' clinical decision making[46] and salaried versus fee-for-service (FFS) reimbursement has a significant impact on physician behavior[47]. Furthermore, the salary-only model is common among academic health providers[48]. In a previous study,

financial incentives might have played a greater role for urologists without medical school affiliation and who are thus more likely to be paid on a FFS basis rather than salaried[31]. Academic physicians may also have a greater opportunity to partake in a deliberative and shared decision making process[49]. Other characteristics of physicians (e.g. intrinsic motivation, professionalism, altruism) may influence their response to financial incentives[50-54].

The association of urologist characteristics and changes in ADT use is also likely influenced by other externalities. Individual patient selection biases that were not assessed may have led to the observed variability. I acknowledge other important limitations of my SEER-Medicare based study[32]. Patterns of ADT use among the elderly may not be generalizable to other patient population (e.g. younger, privately insured patients and/or those treated in health maintenance organizations) and may not be representative of the urologist's entire practice. Nonetheless, approximately 79% of men with initial prostate cancer are 65 years or older[55] and in 2003, 89% of Medicare beneficiaries were covered under the traditional FFS program[56]. The small number of non-institutional affiliated urologists may have limited my power to detect their differences and ADT trends.

Without specific PSA values recorded by SEER before 2004, my study excluded PSA values. Nonetheless, as pointed out by a previous study[31], patients with higher-risk disease (i.e. higher PSA) would more likely be treated by major academic affiliated urologists; this could lead to a bias towards the null (i.e. greater ADT use by major medical school affiliated urologists) thereby leaving us with valid significant associations. I also acknowledge that some ADT was driven by high PSA levels; however, this is unlikely because in 2002, only 7.3% of patients with clinically localized prostate cancer had PSA levels ≥20 ng/mL[57]. Furthermore, published data from the CaPSURE database,

which included information on PSA, still showed decreasing primary ADT among low-risk patients from 2000-2007, thereby mirroring my study's overall trends[29]. Moreover, after adjusting for clinical variables like stage and grade, differences in PSA levels across urologist characteristics should be minimized.

The changes in SEER's definition of intermediate grade tumor (i.e. from Gleason score 4-7 prior to 2003 to Gleason score 4-6 from 2003 onwards) likely led to variability in the 2003 observations when compared to pre-2003 years but not when compared to post-2003 years[22]. Additionally, as pointed out by previous studies[22,58], there is a grade migration trend in recent years, which could lead to lower ADT use. Future studies should investigate the effects of grade migration on ADT utilization rates among urologists with different levels of medical school affiliations.

Part of the downward ADT utilization trend may be influenced by publications addressing multiple ADT-associated adverse effects[14-18,20,59,60] and patients' quality of life[19]. However, even with strong level-1 clinical evidence, there is considerable lag time in translation from clinical evidence discovery to clinical practice[61,62].

Annual guidelines by the National Comprehensive Cancer Network since 1996 that recommended ADT as initial therapy for clinical stage T3-T4 or metastatic prostate cancer remained mostly consistent throughout the study period[6-11,13]. Nonetheless, the lack of uniform guidelines, published by the American Urological Association[21,63] and the American Society of Clinical Oncology[12], that address the clinical scenario investigated may account for the observed variability in ADT trends. Clinical guidelines can have limited impact on physician behavior[64-66]. However, my results support previous findings that higher quality of care and better guideline compliance are found in academic settings versus non-academic settings[67-70].

Before and during the study period, there were ongoing ADT-drug-related federal investigations and convictions involving pharmaceutical companies and urologists regarding violations of the Prescription Drug Marketing Act and the False Claims Act[26,71,72]. The high profile nature of these fraud cases may have inadvertently led to variability in guideline discordant ADT utilization before and after the MMA reimbursement changes. My findings suggest that MMA passage contributed to reducing guideline discordant ADT levels that otherwise could have been higher in the absence of the MMA.

ADT reimbursement reductions following MMA passage also coincided with initiation of Medicare reimbursement for Intensity Modulated Radiation Therapy (IMRT), an expensive form of radiation therapy. The mean 2005 reimbursement per Medicare patient for IMRT topped USD31k[73] and approached USD50k[74,75], whereas the mean 2005 monthly reimbursement per dose of ADT fell to USD176. The huge reimbursement differential between the two treatments may have provided an income substitute[76,77] due to loss of post-MMA ADT revenue, especially for FFS non-medical school affiliated urologists. The emergence of IMRT may have accentuated the shift from ADT use post-MMA and hence partially explain why physician-induced demand or the target income hypothesis[78-85] has not led to increased ADT utilization post-MMA.

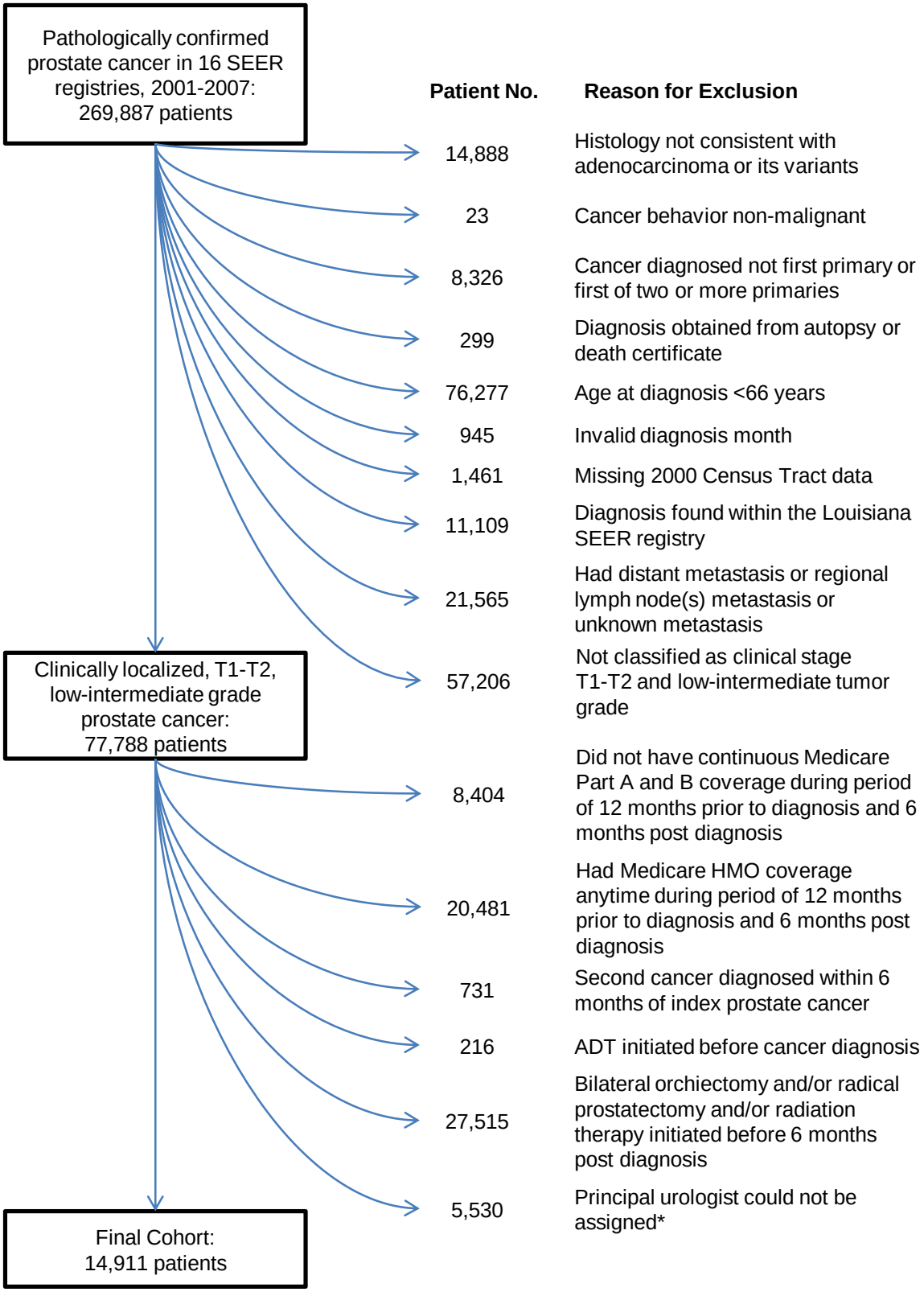


Figure 5.1 Definition of study cohort of 14,911 men with clinically localized, T1-T2, low-intermediate grade prostate cancer. HMO, Health Maintenance Organization; SEER, Surveillance, Epidemiology and End Results; ADT, Androgen Deprivation Therapy, *Resulting from adoption of criteria developed by Shahinian et al.[31]

Table 5.1 Percentage of patients receiving ADT within 6 months after prostate cancer diagnosis according to their clinical and sociodemographic characteristics, and the characteristics of their urologists

		No.	% of patients receiving ADT	P***
All patients		14,911	36.6	
Patient Sociodemographic Characteristics				
Age at Diagnosis				<.0001
	66-69	2,372	29.3	
	70-74	3,690	35.0	
	75-79	4,375	35.7	
	80-84	3,104	41.5	
	≥85	1,370	44.9	
Race/ Ethnicity				<.0001
	Non-Hispanic White	11,343	35.5	
	Non-Hispanic Black	1,204	42.7	
	Hispanic	964	41.9	
	Non-Hispanic Asian/ Pacific Islander	558	42.1	
	Other/ Unknown	842	32.7	
Marital Status				.001
	Married	8,911	35.7	
	Not Married	3,113	36.3	
	Unknown	2,887	39.5	
SEER Region of Residence				<.0001
	Georgia	477	35.2	
	California	5,048	33.3	
	Connecticut	890	31.7	
	Detroit	1,461	40.5	
	Hawaii	124	41.1	
	Iowa	1,000	40.9	
	Kentucky	1,163	40.4	
	New Jersey	2,582	46.3	
	New Mexico	416	27.2	
	Seattle	1,053	28.7	
	Utah	697	27.1	
Rural Status				.746
	Non-Rural	14,639	36.5	
	Rural	272	37.5	
Census Tract: Percentage of Adults with Less than High School Education				<.0001
	<7.7	3,489	30.7	
	7.7 - <13.50	3,621	34.2	
	13.50 - <22.40	3,762	38.1	
	≥22.40	4,039	42.3	
Census Tract: Median Income (USD)				<.0001
	<36,900	4,117	41.0	
	36,900 - <49,500	3,828	37.1	
	49,500 - <66,700	3,629	35.4	
	≥66,700	3,337	31.9	

Table 5.1. Percentage of patients receiving ADT within 6 months after prostate cancer diagnosis according to their clinical and sociodemographic characteristics, and the characteristics of their urologists (continued)

		No.	% of patients receiving ADT	P***
Patient Clinical Characteristics				
Comorbidity Index*				.093
	0	8,533	36.1	
	1	3,844	38.1	
	2	1,440	34.9	
	≥3	1,094	37.1	
Clinical Tumor Stage				<.0001
	T1	7,651	30.1	
	T2	7,260	43.3	
Tumor Grade**				<.0001
	Low	735	18.0	
	Intermediate	14,176	37.5	
Year of Diagnosis				<.0001
	2001	2,576	45.2	
	2002	2,997	44.6	
	2003	2,474	42.1	
	2004	1,839	34.6	
	2005	1,690	28.5	
	2006	1,732	25.8	
	2007	1,603	21.5	

Table 5.1. Percentage of patients receiving ADT within 6 months after prostate cancer diagnosis according to their clinical and sociodemographic characteristics, and the characteristics of their urologists (continued)

		No.	% of patients receiving ADT	P***
Urologist Characteristics				
Age				<.0001
	<42	3,437	32.9	
	42-50	4,358	38.8	
	51-57	3,796	36.7	
	>57	3,320	37.2	
Sex				.118
	Male	14,769	36.6	
	Female	142	30.3	
Board Certification				<.0001
	Yes	13,949	35.8	
	No	962	47.4	
US Trained				<.0001
	Yes	12,396	34.8	
	No	2,515	45.2	
Degree Type				.715
	MD	14,594	36.5	
	DO	317	37.5	
Years After Medical School Graduation				<.0001
	<17	3,661	32.8	
	17-24	4,084	39.3	
	25-32	3,789	36.2	
	>32	3,377	37.8	
No. of Patients				.012
	<38	3,572	35.9	
	38-59	3,908	36.7	
	60-82	3,815	35.1	
	>82	3,616	38.6	
Medical School Affiliation				<.0001
	Major	797	29.2	
	Mixed	11,447	36.4	
	None	2,636	39.3	
	Non-Institutional	31	32.3	

Abbreviations: ADT, Androgen Deprivation Therapy; DO, Doctor of Osteopathy; MD, Doctor of Medicine; SEER, Surveillance, Epidemiology, and End Results; USD, United States Dollar

* Comorbidity Index based on a modification of the Charlson Comorbidity Index

** Intermediate tumor grade corresponds to Gleason score 5-7 in 2001-2002 and Gleason score 5-6 in 2003-2007, Low tumor grade corresponds to Gleason score 2-4 in 2001-2007

*** P values calculated from two-sided χ^2 tests for heterogeneity in proportion of patients receiving ADT across different patient sociodemographic, clinical characteristics and their urologists' characteristics

Table 5.2 Unadjusted univariate and adjusted multivariate multilevel regression models predicting the odds of receiving ADT among clinically localized prostate cancer patients

		Unadjusted		Adjusted	
Characteristics		**OR (95% CI)**	**P*****	**OR (95% CI)**	**P*****
Patient Sociodemographic Characteristics					
Age at Diagnosis					
	66-69	1.00 (Referent)		1.00 (Referent)	
	70-74	1.31 (1.16-1.47)	<.0001	1.32 (1.17-1.50)	<.0001
	75-79	1.34 (1.18-1.51)	<.0001	1.29 (1.13-1.46)	<.0001
	80-84	1.73 (1.51-1.98)	<.0001	1.64 (1.43-1.89)	<.0001
	≥85	2.03 (1.73-2.38)	<.0001	1.98 (1.68-2.33)	<.0001
Race/ Ethnicity					
	Non-Hispanic White	1.00 (Referent)		1.00 (Referent)	
	Non-Hispanic Black	1.29 (1.10-1.50)	.001	1.18 (1.00-1.40)	.054
	Hispanic	1.18 (1.00-1.40)	.058	1.17 (0.97-1.40)	.102
	Non-Hispanic Asian/ Pacific Islander	1.23 (0.98-1.56)	.079	1.30 (1.02-1.65)	.034
	Other/ Unknown	0.91 (0.75-1.09)	.311	0.85 (0.70-1.02)	.077
Marital Status					
	Married	1.00 (Referent)		1.00 (Referent)	
	Not Married	1.03 (0.94-1.13)	.545	0.97 (0.88-1.07)	.525
	Unknown	1.16 (1.04-1.30)	.010	0.98 (0.87-1.11)	.772
SEER Region of Residence					
	Georgia	1.00 (Referent)		1.00 (Referent)	
	California	0.84 (0.60-1.17)	.301	0.78 (0.55-1.10)	.156
	Connecticut	0.83 (0.57-1.23)	.359	0.98 (0.65-1.49)	.939
	Detroit	1.03 (0.70-1.52)	.880	0.90 (0.60-1.37)	.625
	Hawaii	1.08 (0.54-2.16)	.823	0.95 (0.48-1.91)	.889
	Iowa	1.06 (0.70-1.61)	.789	0.93 (0.60-1.44)	.751
	Kentucky	1.25 (0.85-1.84)	.267	1.16 (0.77-1.75)	.481
	New Jersey	1.55 (1.10-2.19)	.012	1.72 (1.19-2.47)	.004
	New Mexico	0.76 (0.44-1.29)	.307	0.65 (0.37-1.14)	.135
	Seattle	0.67 (0.44-1.01)	.055	0.66 (0.43-1.01)	.053
	Utah	0.56 (0.36-0.86)	.008	0.55 (0.35-0.85)	.008
Rural Status					
	Non-Rural	1.00 (Referent)		1.00 (Referent)	
	Rural	1.06 (0.80-1.40)	.686	1.00 (0.74-1.34)	.980
Census Tract: Percentage of Adults with Less than High School Education					
	<7.7	1.00 (Referent)		1.00 (Referent)	
	7.7 - <13.50	1.06 (0.95-1.19)	.276	1.00 (0.88-1.13)	.984
	13.50 - <22.40	1.18 (1.05-1.32)	.005	1.04 (0.90-1.20)	.595
	≥22.40	1.42 (1.26-1.60)	<.0001	1.12 (0.94-1.34)	.196
Census Tract: Median Income (USD)					
	<36,900	1.00 (Referent)		1.00 (Referent)	
	36,900 - <49,500	0.83 (0.75-0.93)	.001	0.89 (0.78-1.01)	.075
	49,500 - <66,700	0.76 (0.68-0.85)	<.0001	0.86 (0.73-1.00)	.044
	≥66,700	0.70 (0.62-0.80)	<.0001	0.81 (0.67-0.97)	.024

Table 5.2. Unadjusted univariate and adjusted multivariate multilevel regression models predicting the odds of receiving ADT among clinically localized prostate cancer patients (continued)

Characteristics		Unadjusted OR (95% CI)	P***	Adjusted OR (95% CI)	P***
Patient Clinical Characteristics					
Comorbidity Index*					
	0	1.00 (Referent)		1.00 (Referent)	
	1	1.04 (0.95-1.13)	.384	1.00 (0.92-1.10)	.974
	2	0.96 (0.84-1.09)	.517	0.94 (0.82-1.08)	.406
	≥3	0.98 (0.84-1.13)	.730	0.97 (0.83-1.13)	.692
Clinical Tumor Stage					
	T1	1.00 (Referent)		1.00 (Referent)	
	T2	1.85 (1.69-2.01)	<.0001	1.61 (1.47-1.76)	<.0001
Tumor Grade**					
	Low	1.00 (Referent)		1.00 (Referent)	
	Intermediate	3.06 (2.48-3.77)	<.0001	3.59 (2.90-4.45)	<.0001
Year of Diagnosis					
	2001	1.15 (1.02-1.31)	.029	1.16 (1.02-1.33)	.022
	2002	1.12 (1.00-1.27)	.046	1.10 (0.97-1.24)	.137
	2003	1.00 (Referent)		1.00 (Referent)	
	2004	0.70 (0.61-0.81)	<.0001	0.72 (0.62-0.83)	<.0001
	2005	0.50 (0.43-0.59)	<.0001	0.53 (0.45-0.62)	<.0001
	2006	0.44 (0.38-0.51)	<.0001	0.46 (0.39-0.54)	<.0001
	2007	0.37 (0.31-0.43)	<.0001	0.39 (0.33-0.45)	<.0001

Table 5.2. Unadjusted univariate and adjusted multivariate multilevel regression models predicting the odds of receiving ADT among clinically localized prostate cancer patients (continued)

Characteristics		Unadjusted OR (95% CI)	P***	Adjusted OR (95% CI)	P***
Urologist Characteristics					
Sex					
	Male	1.00 (Referent)		1.00 (Referent)	
	Female	0.78 (0.54-1.13)	.192	0.90 (0.60-1.34)	.593
Board Certification					
	Yes	1.00 (Referent)		1.00 (Referent)	
	No	1.43 (1.07-1.90)	.016	1.17 (0.83-1.63)	.340
US Trained					
	Yes	1.00 (Referent)		1.00 (Referent)	
	No	1.78 (1.49-2.12)	<.0001	1.50 (1.24-1.81)	<.0001
Degree Type					
	MD	1.00 (Referent)		1.00 (Referent)	
	DO	0.96 (0.64-1.45)	.858	0.77 (0.49-1.23)	.274
Years After Medical School Graduation					
	<17	1.00 (Referent)		1.00 (Referent)	
	17-24	1.26 (1.04-1.51)	.016	1.07 (0.88-1.29)	.512
	25-32	1.25 (1.05-1.49)	.013	0.99 (0.82-1.20)	.917
	>32	1.34 (1.12-1.61)	.001	0.98 (0.81-1.19)	.835
No. of Patients					
	<38	1.00 (Referent)		1.00 (Referent)	
	38-59	1.01 (0.85-1.20)	.911	0.99 (0.83-1.18)	.885
	60-82	0.96 (0.81-1.15)	.661	0.92 (0.77-1.11)	.376
	>82	1.02 (0.84-1.24)	.850	1.01 (0.82-1.24)	.951
Medical School Affiliation					
	Major	1.00 (Referent)		1.00 (Referent)	
	Mixed	1.64 (1.28-2.09)	<.0001	1.92 (1.49-2.47)	<.0001
	None	2.03 (1.55-2.66)	<.0001	2.35 (1.77-3.12)	<.0001
	Non-Institutional	1.64 (0.71-3.80)	.246	1.14 (0.47-2.76)	.767

Abbreviations: ADT, Androgen Deprivation Therapy; CI, Confidence Interval; DO, Doctor of Osteopathy; MD, Doctor of Medicine; OR, Odds Ratio; SEER, Surveillance, Epidemiology, and End Results; USD, United States Dollar

* Comorbidity Index based on a modification of the Charlson Comorbidity Index

** Intermediate tumor grade corresponds to Gleason score 5-7 in 2001-2002 and Gleason score 5-6 in 2003-2007, Low tumor grade corresponds to Gleason score 2-4 in 2001-2007

*** P values calculated from Hierarchical Generalized Linear Mixed Models

Table 5.3 Characteristics of principal urologists who treated patients diagnosed from 2001-2007 with clinically localized prostate cancer

			No.	%
All Urologists			1,943	100.0
Age				
	<42		559	28.8
	42-50		475	24.5
	41-57		445	22.9
	>57		464	23.9
Sex				
	Male		1,892	97.4
	Female		51	2.6
Board Certification				
	Yes		1,813	93.3
	No		130	6.7
US Trained				
	Yes		1,630	83.9
	No		313	16.1
Degree Type				
	MD		1,896	97.6
	DO		47	2.4
Years After Medical School Graduation				
	<17		592	30.5
	17-24		426	21.9
	25-32		457	23.5
	>32		468	24.1
No. of Patients				
	<38		1,018	52.4
	38-59		444	22.9
	60-82		284	14.6
	>82		197	10.1
Medical School Affiliation				
	Major		198	10.2
	Mixed		1,289	66.3
	None		427	22.0
	Non-Institutional		29	1.5
Abbreviations: DO, Doctor of Osteopathy; MD, Doctor of Medicine				

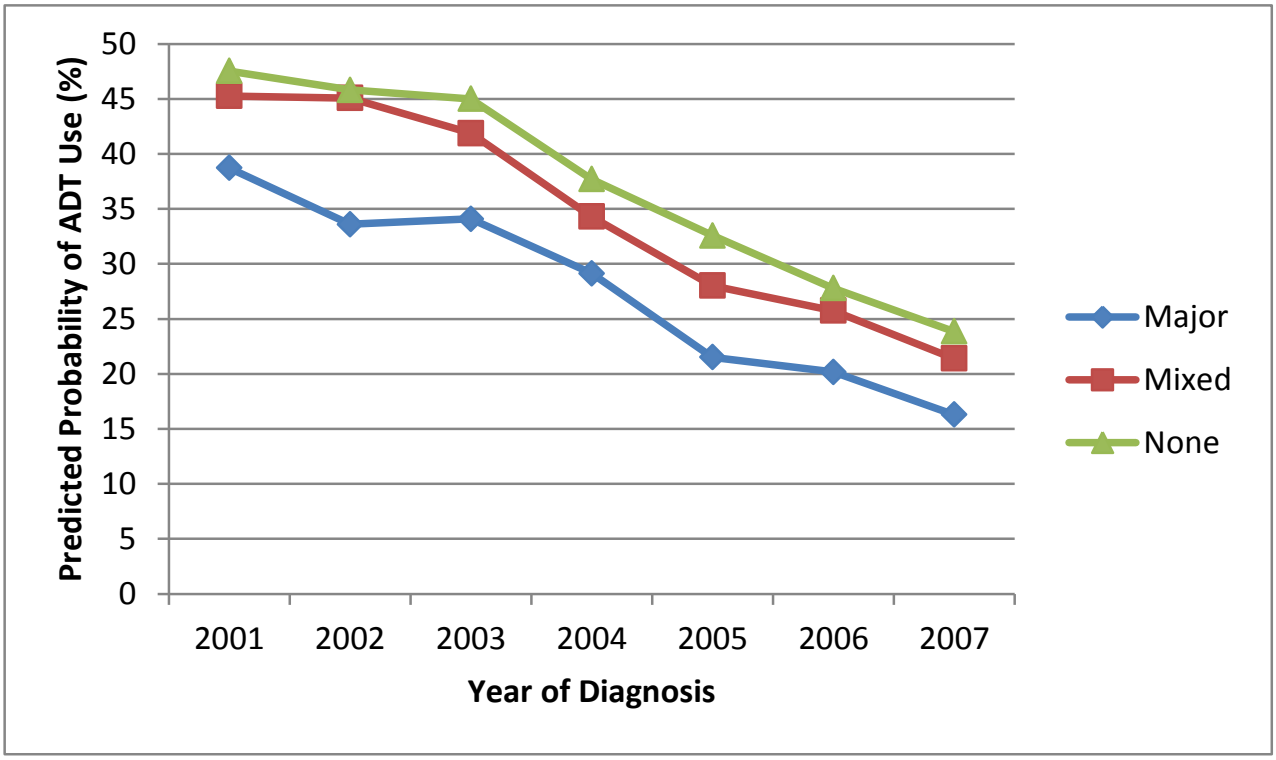


Figure 5.2 Mean predicted probabilities of patient receipt of androgen deprivation therapy (ADT) across different years of diagnosis, adjusted for patient sociodemographic and clinical characteristics and their principal urologists' characteristics, for each category of principal urologists' medical school affiliation

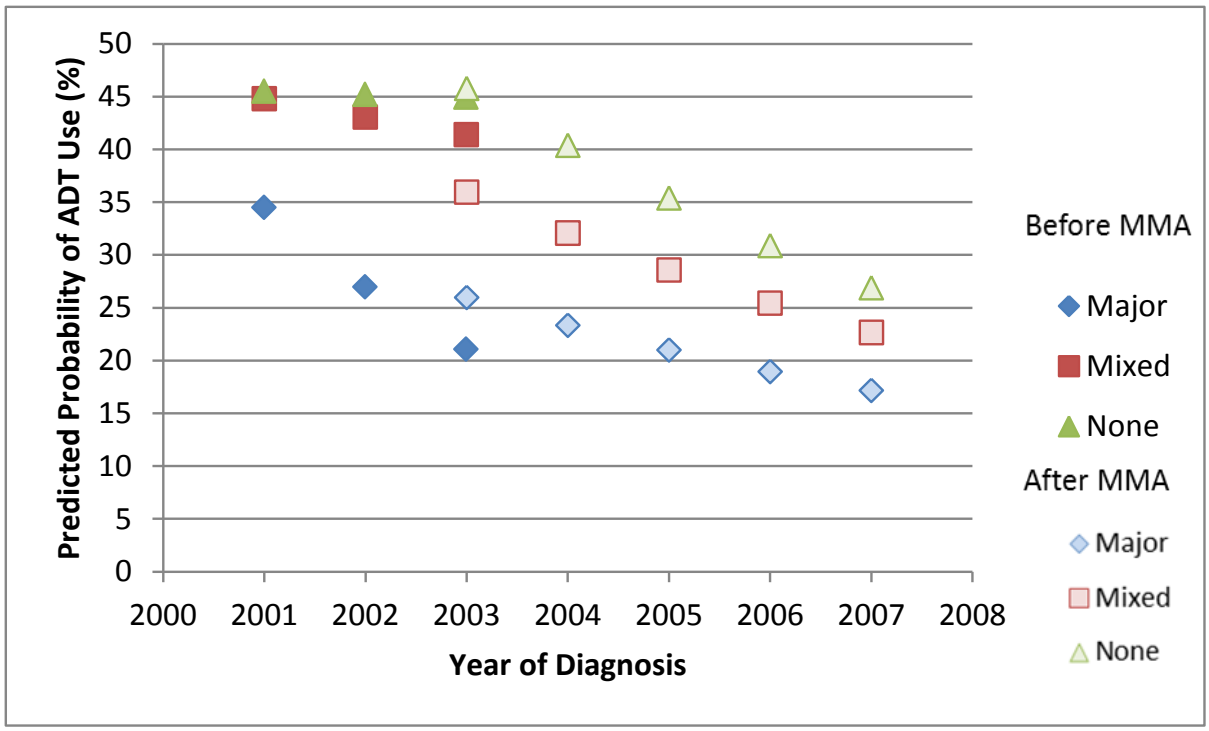


Figure 5.3 Fitted linear regression of predicted probabilities of patient receipt of androgen deprivation therapy (ADT) across different years of diagnosis, adjusted for patient sociodemographic and clinical characteristics and their principal urologists' characteristics, for each category of principal urologists' medical school affiliation

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CHAPTER 6 SECOND ESSAY — ROLE OF THE UROLOGIST IN WHETHER LOCOREGIONAL PROSTATE CANCER PATIENTS CONSULT A RADIATION ONCOLOGIST

Introduction

With insufficient high-quality clinical evidence to support the superiority of one treatment modality over another[1], prostate cancer patients and physicians face difficult decisions regarding treatment choices. For guidance, patients seek information and recommendations from multiple physicians including urologists and radiation oncologists, the two most common specialists involved in prostate cancer care[2]. Urologists generally act as both diagnosticians (e.g. diagnosing patients with prostate cancer after performing diagnostic core needle biopsy) and proceduralists (e.g. performing radical prostatectomy). By contrast, radiation oncologists usually act solely as proceduralists (e.g. administering radiation therapy) during the prostate cancer treatment paradigm. In the US, urologists tend to perform biopsies for patients who are suspected of having prostate cancer and therefore tend to be the first physician to discuss patients' diagnostic, treatment and referral options.

A study comparing treatment recommendations by urologists and radiation oncologists found that physicians overwhelmingly recommended therapy that they themselves deliver[3]. Likewise, studies have found a strong correlation between types of specialist seen and initial treatment received by prostate cancer patients[2,4]. Multiple studies have indicated that physician characteristics are important determinants of patient referral patterns[5-8] and that physicians play a major role in advising and influencing patients' best treatment options[9-14].

In addition, there is a reimbursement differential among treatment options available for prostate cancer patients that could influence treatment recommendations. In 2005, mean reimbursement per Medicare patient for intensity modulated radiation therapy (IMRT), the predominant form of prostate cancer radiation therapy[15], exceeded USD 31k, whereas mean reimbursement for minimally invasive radical prostatectomy was less than USD 17k[16]. Presently, there exists a new wave of integrated prostate cancer centers in which urologists have ownership interests in IMRT equipment[17]. With large initial capital investment costs (approximately USD 3 million[17]) associated with IMRT technology, there may be complex financial incentives for urologists who have IMRT ownership stakes to self-refer patients for radiation oncology consultation within their integrated cancer centers. Such financial incentives may not be present among urologists who work in major medical school affiliated institutions and therefore have no financial need to recoup personal IMRT investment costs by increasing patient throughput.

In this study, I assess the influence of urologists and their medical school affiliation as a determinant of their locoregional prostate cancer patients' subsequent radiation oncologist consultation. I hypothesize that patients diagnosed by urologists with major medical school affiliations are less likely to subsequently consult a radiation oncologist.

Methods

Data Sources

I used the Surveillance, Epidemiology and End Results (SEER)-Medicare database that links cancer registry information in selected U.S. geographic areas with claims for covered health care services of Medicare beneficiaries[18]. For the study period, 2004-2007, incident prostate cancer cases are available from 16 SEER registries. Louisiana SEER registry data was removed from this study due to missing 2005 information following Hurricane Katrina. Data from metropolitan Atlanta and Rural Georgia SEER registries are hereinafter classified as Georgia.

Characteristics of physicians who treated SEER-Medicare patients were obtained from the American Medical Association (AMA) Physician Masterfile.

An analytical cohort of locoregional prostate cancer patients with an identified index urologist was created using the registry-claims linked data. Annual guidelines, published by the National Comprehensive Cancer Network since 1996 and throughout my study period, consistently recommended radiation as a possible treatment option regarding initial therapy for locoregional prostate cancer (any T, any N, M0)[21-27]. Patients with distant metastasis (M1) were excluded. Urologists perform core needle biopsies to detect and diagnose prostate cancer[28]. The Medicare associated Healthcare Common Procedure Coding System (HCPCS) code used to identify diagnostic biopsy is 55700. The urologist who performed the biopsy on the day closest to the patient's diagnosis date in SEER was assigned as the patient's index urologist. Patients who were diagnosed with prostate cancer without undergoing a biopsy, or received their biopsies from a non-urologist, or had multiple biopsies performed by different urologists on the day closest to the patient's diagnosis date were removed. These exclusions were

intended to create a more homogenous population in terms of treatment selection. All additional exclusion criteria are detailed in Figure 6.1.

Institutional review board approval was obtained from Morehouse School of Medicine and Emory University.

Patient Characteristics

Sociodemographic and clinical characteristics of the analytic cohort are presented in Table 6.1. Race, ethnicity, age at diagnosis, marital status, rural status, SEER region of residence, year of diagnosis, clinical tumor size/extension (TNM T component), regional lymph node metastasis (TNM N component), tumor grade (low, Gleason grade 2 - 4; intermediate, Gleason grade 5 - 6; high, Gleason grade 7 - 10)[29] and prostate specific antigen (PSA) levels at time of diagnosis were extracted from SEER files. Education and income levels were based on US Census tract data from 2000; the categories chosen were pre-specified to ensure a reasonable distribution with cutoffs approximately corresponding to quartiles. The prevalence of comorbid disease in my study cohort is calculated using a modified Charlson comorbidity index derived from Medicare Part A and Part B claims[30,31]. Specifically, International Classification of Diseases, Ninth Revision, Clinical Modification codes consistent with comorbidities of interest were weighted and examined from one year before to one month after diagnosis.

Urologist Characteristics

Urologists were identified by using either the Health Care Financing Administration (HCFA) specialty codes in Medicare claims, the physician specialty (primary or secondary) information from the AMA Physician Masterfile or the urology board certification identified through the ABMS information within the AMA Physician Masterfile. Other urologist characteristics extracted from the AMA Physician Masterfile included age, gender, years after medical school graduation, location of training (US or otherwise), type of degree [Doctor of Medicine (MD) or Doctor of Osteopathy (DO)] and the urology board certification (Table 6.1). Urologists' patient volume is defined as the number of unique prostate cancer patients that each urologist saw during the study period. The categories used for the urologists' patient volume, age, and years after medical school graduation were pre-specified to ensure cutoffs approximately corresponding to quartiles.

Urologist Medical School Affiliation

Source files for key variables used to categorize the urologist medical school affiliation are summarized in Figure 3.3 in Chapter 3. Urologists' medical school affiliation is derived from the SEER-Medicare Hospital (HOSP) file. Specifically, if the Medicare biopsy claim recorded in the institutional outpatient standard analytical file (OUTSAF) was submitted from a hospital with a *major* or *without* a medical school affiliation (as defined within the HOSP file), the associated index urologist was categorized as having a *major* or *no* medical school affiliation respectively. Index urologists were categorized as having *mixed* medical school affiliations if the OUTSAF biopsy claims were from hospitals with limited or graduate medical school affiliations[32].

Some biopsy claims were found within the National Claims History (NCH) file (consisting of mostly non-institutional physician/ supplier claims) which does not have an associated provider (e.g. hospital) identifier that is required to retrieve the medical school affiliation (found within HOSP) of the index urologist. Such NCH claims were assigned the provider identifier associated with the institutional inpatient Medicare Provider Analysis and Review (MEDPAR) claims if 1) the patient associated with both types of claims matched, 2) the NCH place of service was institutional[33] and 3) the NCH claims dates fell between the MEDPAR admission and discharge dates.

Subsequently, for the remaining NCH biopsy claims that cannot be assigned provider identifiers from MEDPAR claims, they are assigned with provider identifiers from OUTSAF claims if 1) the patient and the urologist associated with both types of claims matches, 2) the NCH place of service is institutional[33] and 3) the NCH claims dates fall between the OUTSAF claims dates. Urologists whose biopsy claims can only be found in the NCH file and whose claims cannot be assigned with provider identifiers from claims found in either the OUTSAF or MEDPAR (as described previously) were categorized as having a *non-institutional* affiliation.

Measurement of Outcomes

Radiation oncologists were identified using either the HCFA specialty codes, the AMA Physician Masterfile's physician specialty information or the ABMS radiation oncology board certification information. A patient was identified and categorized as having a radiation oncologist consultation if that he had at least one radiation oncologist associated Medicare claim within 9 months after locoregional prostate cancer diagnosis.

Statistical Analyses

The differences in proportion of patients consulting radiation oncologists across index urologist and patient characteristics are evaluated using χ^2 tests. The effect of patient and urologist characteristics on the likelihood of a subsequent radiation oncologist consultation was assessed with logistic hierarchical generalized linear mixed models[34] (GLMM) and estimated using the restricted pseudo-likelihood methodology[34-36]. The use of hierarchical GLMM accounted for the possible clustering of subsequent radiation oncologist consultation among patients who had the same index urologist who performed their diagnostic biopsies. The unit of analysis was the patient. The clustering variable was the index urologist associated with each patient. Univariate and adjusted multivariate odds ratio (ORs) and 95% confidence intervals (CIs) for the radiation oncologist consultation were calculated for each patient and urologist characteristic (Table 6.2).

In order to estimate the percentage of total variance in the patient's subsequent radiation oncologist consultation attributable to the patient's index urologist, I estimated the intraclass correlation coefficient (ICC) from hierarchical GLMM using the threshold method[37]. Both a null model, excluding patient and urologist characteristics, and adjusted models, which included all these characteristics, were constructed. From the adjusted models, the residual ICC, representing the percentage of variance attributable to the index urologist after adjustments, was calculated. All statistical testing was two-sided, performed at 5% significance level, and used SAS version 9.3 (SAS Institute, Cary, NC).

Results

The SEER-Medicare database contained 39,934 men diagnosed with incident locoregional prostate cancer from 2004-2007 who met study eligibility criteria. A total of 2,405 urologists performed diagnostic biopsies on these patients. These urologists are predominantly male (96.8%), board certified (93.4%), had a patient volume across the study period of less than 37 (60.5%), were trained in the U.S. (84.4%) and are MD (97.6%) as opposed to DO degrees holders (Table 6.3).

Table 6.1 shows the percentages of patients who subsequently consulted a radiation oncologist by their sociodemographic, clinical and index urologists' characteristics. Overall, 25,117 (62.9%) patients consulted a radiation oncologist within 9 months following prostate cancer diagnosis. Radiation oncologist consultations are less common among patients who are 80 years or older, of Hispanic ethnicity, unmarried, residing in SEER areas covering Iowa, New Mexico or Utah, and residing in census tracts with lower educational and median incomes levels. Consultations were also less common among patients with higher levels of comorbidities, tumor stages higher than T1, PSA levels higher than 20 ng/mL, low tumor grade, and/or positive regional lymph nodes. Index urologists associated with patients who consulted radiation oncologists are more likely to be older than 57 years, have a patient volume less than 37, be trained in the U.S. and/or have a mixed medical school affiliation.

Using hierarchical GLMM analyses, I investigated factors associated with patients' subsequent radiation oncologist consultation following their diagnosis, while controlling for the fact that multiple patients might be diagnosed by the same urologist (Table 6.2). As the unadjusted odds ratios show, lower propensities to consult radiation oncologists are associated with patients 80 years or older, of Hispanic ethnicity as compared to

Whites, who were unmarried, residing in California, Iowa, Kentucky, New Mexico or Utah as compared to Georgia, and residing in census tracts with lower education and/or median income levels. The same association was also observed for patients with higher levels of comorbidities, clinical stage T2 –T4 as compared to T1, regional lymph node metastasis stage N1 as compared to N0, low as compared to high grade tumor and higher PSA levels. Patients who subsequently consult radiation oncologists are significantly associated with index urologists who have a non-institutional affiliation (odds ratio [OR], 1.21; 95% confidence interval [95% CI], 1.02-1.44, p=0.03) when compared to those with major medical school affiliations. When compared with major medical school affiliated urologists, insignificant associations were found regarding radiation oncologist consultations among patients diagnosed by urologists with mixed or no medical school affiliations.

After adjusting for patient and urologist characteristics, subsequent radiation oncologist consultation remained significantly associated with patients whose index urologists had non-institutional affiliations (OR, 1.41; 95% CI, 1.18-1.70, p=0.0002) as opposed to major medical school affiliations. In addition, patients who subsequently consulted radiation oncologists were also significantly more likely to be diagnosed by index urologists who were older than 57 years (OR, 1.22; 95% CI, 1.08-1.39, p=0.002).

As a measure of the overall influence of the index urologist on the patient's subsequent radiation oncologist consultation, I estimated the ICC. In the null model, with no predictors included, it is assumed that the probability of the subsequent radiation oncologist consultation does not vary by individual patient or index urologist characteristics. Using the null model, I estimated that 18.2% of the variance in subsequent radiation oncologist consultation was attributable to the index urologist. After

adjusting for patient and index urologist characteristics listed in Table 6.2, the variance attributable to the index urologist decreased slightly to 18.0%.

Discussion

To my knowledge, this is the first study to investigate the role of the urologist on the likelihood of subsequent radiation oncologist consultation by men diagnosed with locoregional prostate cancer. In addition, this is the first study that uses Medicare inpatient, outpatient and non-institutional claims to categorize urologists' medical school affiliations. My findings showed that urologists accounted for approximately 18% of variation in the likelihood of patients' subsequent radiation oncologist consultations. The index urologists' age and their non-institutional practice affiliation exerted a significant influence on their diagnosed patients' subsequent radiation oncologist consultations. Similar radiation oncologist consultation patterns were found among patients diagnosed by institutional affiliated urologists regardless of their level of medical school affiliations. Other significant associations found between radiation oncologist consultations and patient-related sociodemographic and clinical factors complement prior research[2].

The significant associations with urologist age may be a result of younger urologists being keener to act as proceduralists (e.g. performing radical prostatectomy) and hence not actively referring their diagnosed patients to a radiation oncologist. There are also inherent differences between physicians practicing within major medical schools and non-institutional settings that may explain the variations observed.

First, physicians working for academic health providers are more commonly remunerated through a salary-only payment mechanism rather than a fee-for-service (FFS) model[38]. Previous research showed that different payment mechanisms do influence clinical decision making[39] and physician behavior is significantly different under salaried versus FFS reimbursement models. A previous study concluded that, regarding inappropriate androgen deprivation therapy use, financial incentives might have played a

lesser role for major medical school affiliated urologists since they were more likely to be salaried[40].

Second, urologists practicing in non-institutional settings may have a higher likelihood of personal capital investments in radiation oncology equipment. A study found that radiation therapy facilities with ownership interest by non-radiation oncologists performed 58% more procedures than did facilities without ownership conflicts[41] . Another study found that the likelihood of patients receiving radiation increased more than 16-fold if they saw a urologist and a radiation oncologist[2]. Such studies may help explain my findings that showed a significant greater propensity of patient's radiation oncologist consultation after being diagnosed by non-institutional affiliated urologists. The significant differences in the patient's subsequent radiation oncologist consultation as a function of their diagnostic index urologists' medical school affiliation may be an amalgamation of any or all of these factors.

Due to SEER-Medicare data limitations, I am unable to directly ascertain individual physicians' payment mechanisms (i.e. salaried versus non-salaried) and if self-referral took place (i.e. if the radiation oncologists that the index urologists' patients subsequently saw were also working within the same urologists' practice; and if the urologist had a financial interest in the referral process). Nonetheless, a 2012 report by the US Government Accountability Office (GAO), that investigated advanced imaging services self-referral concerns, noted "financial incentive for providers to self-refer is most direct when the service is performed in a physician office"[42]. In my study, over 90% of the patients diagnosed by non-institutional affiliated urologists received their biopsies in physician office settings. The GAO report also found that between 2004-2010, the second highest increase in computed tomography self-referral rates occurred among urology providers[42].

I acknowledge other important study limitations when using the SEER-Medicare database[18]. Multiple characteristics of individual physicians (e.g. intrinsic motivation, professionalism, altruism), not measured in this study, may influence their practice pattern or response to financial incentives[43-47]. Medicare claims-based categorization of urologists' medical school affiliation may be influenced by other patients seen (e.g. younger patients, those with private insurance and/or receiving care in health maintenance organization) and therefore my study observations may not be representative of the index urologists' entire practice. Nonetheless, 79% of men with incident prostate cancer are 65 years or older[48] and in 2003, 89% of Medicare beneficiaries were covered under the traditional FFS program[49].

Whether or not a patient sees a radiation oncologist is likely influenced by a multitude of factors. Individual patient selection biases not assessed may have led to variability in observations. It is unclear if my observations reflect urologists' referral decisions or patients' individual choices. Nonetheless, previous studies that indicated the major role physicians play in advising and influencing prostate cancer patients regarding their best treatment options[9-14] would suggest that patient preference is unlikely to entirely explain the observed radiation oncologist consultation patterns. Further research would be necessary to confirm if subsequent radiation oncologist consultation reflect index urologist referral behavior, patient response, or urologist-patient interactions.

Without a gold standard for prostate cancer treatment, urologists' recommendations and referrals can be crucial in determining patients' eventual treatment modality. The inherent differences in specialty-related treatment recommendations[3] suggest that it may be beneficial for patients to seek opinions from different types of specialists before deciding on a specific treatment modality. Ideally, variations observed in this study

should be due to the collective preferences and consents from well informed patients and patient-centered clinical judgment of their urologists.

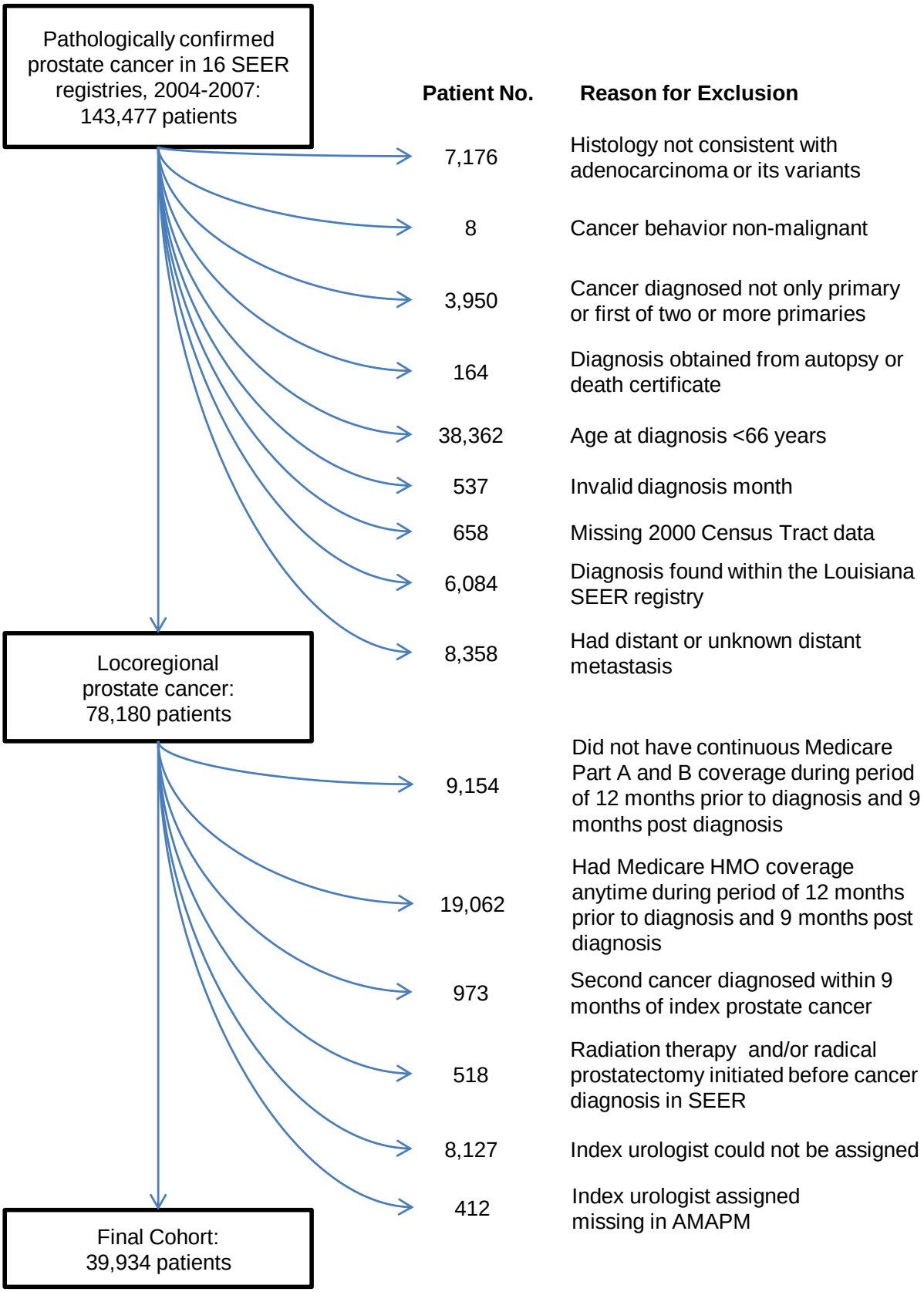

Figure 6.1 Definition of study cohort of 39,934 men with locoregional prostate cancer. HMO, Health Maintenance Organization; SEER, Surveillance, Epidemiology and End Results; AMAPM, American Medical Association Physician Masterfile

Table 6.1 Percentage of patients consulting a radiation oncologist within 9 months after prostate cancer diagnosis by an index urologist, according to the patients' clinical and sociodemographic characteristics, and the characteristics of their index urologists

		No.	% of patients consuting radiation oncologist	P**
All patients		39,934	62.9	
Patient Sociodemographic Characteristics				
Age at Diagnosis				<.0001
	66-69	10,837	60.2	
	70-74	12,784	70.2	
	75-79	9,553	69.3	
	80-84	4,891	51.1	
	≥85	1,869	27.1	
Race/ Ethnicity				<.0001
	Non-Hispanic White	31,073	64.5	
	Non-Hispanic Black	2,916	63.5	
	Hispanic	2,649	56.8	
	Non-Hispanic Asian/ Pacific Islander	1,758	65.5	
	Other/ Unknown	1,538	37.7	
Marital Status				<.0001
	Married	27,344	66.1	
	Not Married	7,393	63.9	
	Unknown	5,197	44.4	
SEER Region of Residence				<.0001
	Georgia	1,608	66.1	
	California	13,452	59.8	
	Connecticut	2,659	73.3	
	Detroit	3,421	62.9	
	Hawaii	721	72.7	
	Iowa	2,377	54.5	
	Kentucky	2,919	61.3	
	New Jersey	7,070	71.7	
	New Mexico	961	49.7	
	Seattle	3,085	61.2	
	Utah	1,661	52.1	
Rural Status				.151
	Non-Rural	39,265	62.9	
	Rural	669	60.2	
Census Tract: Percentage of Adults with Less than High School Education				<.0001
	<7.5	10,031	64.7	
	7.5 - <13.30	10,010	64.4	
	13.30 - <21.60	9,923	62.4	
	≥22.60	9,970	60.1	
Census Tract: Median Income (USD)				<.0001
	<37.400	9,961	59.4	
	37.400 - <50,500	10,007	61.0	
	50,500 - <67,700	9,972	64.5	
	≥67,700	9,994	66.7	

Table 6.1. Percentage of patients consulting a radiation oncologist within 9 months after prostate cancer diagnosis by an index urologist, according to the patients' clinical and sociodemographic characteristics, and the characteristics of their index urologists (continued)

		No.	% of patients consuting radiation oncologist	P**
Patient Clinical Characteristics				
Comorbidity Index*				.001
	0	24,856	63.3	
	1	9,711	63.1	
	2	3,197	61.2	
	≥3	2,170	59.5	
Clinical Tumor Stage				<.0001
	T1	17,153	75.2	
	T2	20,074	54.0	
	T3	2,310	51.3	
	T4	184	56.5	
	Unknown	213	41.3	
Regional Lymph Node Metastasis Stage				.004
	N0	38,937	63.0	
	N1	306	54.9	
	NX/ Unknown	691	59.9	
Tumor Grade				<.0001
	Low	235	52.8	
	Intermediate	17,230	64.5	
	High	21,753	62.2	
	Unknown	716	47.1	
PSA Level at Diagnosis (ng/mL)				<.0001
	0.1-9.9	24,332	68.1	
	10.0-20.0	6,395	65.2	
	>20.0	3,501	57.3	
	Unknown	5,706	41.3	
Year of Diagnosis				.135
	2004	10,268	62.7	
	2005	9,606	62.7	
	2006	10,160	63.8	
	2007	9,900	62.3	

Table 6.1. Percentage of patients consulting a radiation oncologist within 9 months after prostate cancer diagnosis by an index urologist, according to the patients' clinical and sociodemographic characteristics, and the characteristics of their index urologists (continued)

		No.	% of patients consuting radiation oncologist	P**
Urologist Characteristics				
Age				<.0001
	<43	9,983	62.3	
	43-50	10,763	63.7	
	51-57	9,259	60.8	
	>57	9,929	64.6	
Sex				.144
	Male	39,535	62.9	
	Female	399	66.4	
Board Certification				.070
	Yes	37,608	63.0	
	No	2,326	61.1	
US Trained				.002
	Yes	34,155	63.2	
	No	5,779	61.0	
Degree Type				.203
	MD	38,870	62.8	
	DO	1,064	64.8	
Years after Medical School Graduation				.054
	<16	9,856	63.0	
	16-24	11,771	62.6	
	25-31	8,342	62.1	
	>31	9,965	63.9	
No. of Patients				.001
	<37	9,657	64.4	
	38-55	10,500	62.9	
	56-78	10,231	62.6	
	>78	9,546	61.7	
Medical School Affiliation				<.0001
	Major	1,251	61.9	
	Mixed	1,137	67.5	
	None	1,692	56.6	
	Non-Institutional	35,854	63.1	

Abbreviations: DO, Doctor of Osteopathy; MD, Doctor of Medicine; PSA, Prostate Specific Antigen; SEER, Surveillance, Epidemiology, and End Results; USD, United States Dollar

* Comorbidity Index based on a modification of the Charlson Comorbidity Index

** P values calculated from two-sided χ^2 tests for heterogeneity in proportion of patients consulting a radiation oncologist across different patient sociodemographic, clinical characteristics and their index urologists' characteristics

Table 6.2 Unadjusted univariate and adjusted multivariate multilevel regression models predicting odds of consulting a radiation oncologist among locoregional prostate cancer patients

Characteristics		Unadjusted OR (95% CI)	P**	Adjusted OR (95% CI)	P**
Patient Sociodemographic Characteristics					
Age at Diagnosis					
	66-69	1.00 (Referent)		1.00 (Referent)	
	70-74	1.59 (1.49-1.69)	<.0001	1.54 (1.44-1.64)	<.0001
	75-79	1.47 (1.36-1.59)	<.0001	1.46 (1.35-1.58)	<.0001
	80-84	0.62 (0.56-0.68)	<.0001	0.64 (0.58-0.71)	<.0001
	≥85	0.19 (0.17-0.22)	<.0001	0.21 (0.18-0.25)	<.0001
Race/ Ethnicity					
	Non-Hispanic White	1.00 (Referent)		1.00 (Referent)	
	Non-Hispanic Black	0.98 (0.89-1.09)	.732	0.90 (0.81-1.00)	.056
	Hispanic	0.75 (0.69-0.83)	<.0001	0.77 (0.69-0.86)	<.0001
	Non-Hispanic Asian/ Pacific Islander	0.88 (0.76-1.01)	.074	0.86 (0.74-1.00)	.045
	Other/ Unknown	0.35 (0.30-0.39)	<.0001	0.51 (0.44-0.59)	<.0001
Marital Status					
	Married	1.00 (Referent)		1.00 (Referent)	
	Not Married	0.89 (0.84-0.95)	.0002	0.97 (0.91-1.03)	.337
	Unknown	0.36 (0.32-0.40)	<.0001	0.51 (0.46-0.57)	<.0001
SEER Region of Residence					
	Georgia	1.00 (Referent)		1.00 (Referent)	
	California	0.70 (0.56-0.87)	.001	0.81 (0.64-1.02)	.067
	Connecticut	1.39 (1.09-1.79)	.009	1.41 (1.09-1.83)	.010
	Detroit	0.78 (0.60-1.02)	.072	1.34 (1.00-1.80)	.052
	Hawaii	1.30 (0.87-1.94)	.196	2.09 (1.38-3.16)	.001
	Iowa	0.54 (0.41-0.71)	<.0001	0.67 (0.50-0.88)	.005
	Kentucky	0.75 (0.57-0.97)	.030	0.92 (0.69-1.22)	.552
	New Jersey	1.23 (0.97-1.55)	.088	1.47 (1.15-1.89)	.002
	New Mexico	0.50 (0.35-0.72)	.0001	0.75 (0.52-1.09)	.131
	Seattle	0.81 (0.61-1.07)	.135	1.09 (0.81-1.48)	.569
	Utah	0.49 (0.36-0.66)	<.0001	0.59 (0.43-0.81)	.001
Rural Status					
	Non-Rural	1.00 (Referent)		1.00 (Referent)	
	Rural	0.92 (0.77-1.10)	.365	1.05 (0.87-1.26)	.631
Census Tract: Percentage of Adults with Less than High School Education					
	<7.5	1.00 (Referent)		1.00 (Referent)	
	7.5 - <13.30	0.95 (0.89-1.01)	.101	0.93 (0.87-1.01)	.072
	13.30 - <21.60	0.87 (0.82-0.93)	<.0001	0.87 (0.80-0.95)	.002
	≥22.60	0.80 (0.75-0.86)	<.0001	0.83 (0.75-0.92)	.001
Census Tract: Median Income (USD)					
	<37,400	1.00 (Referent)		1.00 (Referent)	
	37,400 - <50,500	1.10 (1.03-1.17)	.005	1.02 (0.94-1.10)	.710
	50,500 - <67,700	1.19 (1.11-1.27)	<.0001	1.00 (0.91-1.09)	.947
	≥67,700	1.29 (1.20-1.40)	<.0001	0.97 (0.87-1.09)	.608

Table 6.2. Unadjusted univariate and adjusted multivariate multilevel regression models predicting odds of consulting a radiation oncologist among locoregional prostate cancer patients (continued)

Characteristics		Unadjusted OR (95% CI)	P**	Adjusted OR (95% CI)	P**
Patient Clinical Characteristics					
Comorbidity Index*					
	0	1.00 (Referent)		1.00 (Referent)	
	1	0.98 (0.93-1.04)	.508	1.01 (0.95-1.06)	.839
	2	0.91 (0.83-0.99)	.030	0.95 (0.87-1.04)	.251
	≥3	0.85 (0.77-0.94)	.001	0.95 (0.85-1.06)	.330
Clinical Tumor Stage					
	T1	1.00 (Referent)		1.00 (Referent)	
	T2	0.40 (0.38-0.43)	<.0001	0.41 (0.38-0.43)	<.0001
	T3	0.39 (0.35-0.43)	<.0001	0.30 (0.26-0.33)	<.0001
	T4	0.51 (0.37-0.71)	<.0001	0.51 (0.36-0.73)	.0003
	Unknown	0.23 (0.17-0.31)	<.0001	0.43 (0.30-0.61)	<.0001
Regional Lymph Node Metastasis Stage					
	N0	1.00 (Referent)		1.00 (Referent)	
	N1	0.72 (0.57-0.90)	.004	1.05 (0.80-1.38)	.718
	NX/ Unknown	0.94 (0.87-1.01)	.095	1.06 (0.96-1.18)	.260
Tumor Grade					
	Low	0.58 (0.44-0.76)	.0001	0.48 (0.35-0.66)	<.0001
	Intermediate	1.06 (1.01-1.12)	.021	0.84 (0.80-0.89)	<.0001
	High	1.00 (Referent)		1.00 (Referent)	
	Unknown	0.49 (0.40-0.59)	<.0001	0.59 (0.47-0.74)	<.0001
PSA Level at Diagnosis (ng/mL)					
	0.1-9.9	1.00 (Referent)		1.00 (Referent)	
	10.0-20.0	0.87 (0.82-0.93)	<.0001	0.98 (0.91-1.04)	.454
	>20.0	0.60 (0.55-0.66)	<.0001	0.77 (0.70-0.84)	<.0001
	Unknown	0.26 (0.23-0.28)	<.0001	0.35 (0.32-0.39)	<.0001
Year of Diagnosis					
	2004	1.00 (Referent)		1.00 (Referent)	
	2005	1.00 (0.94-1.07)	.975	0.97 (0.91-1.04)	.384
	2006	1.06 (1.00-1.14)	.067	1.04 (0.97-1.11)	.298
	2007	0.98 (0.92-1.06)	.643	0.94 (0.87-1.01)	.119

Table 6.2. Unadjusted univariate and adjusted multivariate multilevel regression models predicting odds of consulting a radiation oncologist among locoregional prostate cancer patients (continued)

Characteristics		Unadjusted OR (95% CI)	P**	Adjusted OR (95% CI)	P**
Urologist Characteristics					
Sex					
	Male	1.00 (Referent)		1.00 (Referent)	
	Female	1.18 (0.92-1.51)	.190	1.28 (0.96-1.70)	.094
Board Certification					
	Yes	1.00 (Referent)		1.00 (Referent)	
	No	0.87 (0.72-1.06)	.167	0.87 (0.67-1.13)	.287
US Trained					
	Yes	1.00 (Referent)		1.00 (Referent)	
	No	0.87 (0.76-1.00)	.050	0.92 (0.79-1.07)	.262
Degree Type					
	MD	1.00 (Referent)		1.00 (Referent)	
	DO	1.06 (0.82-1.36)	.681	1.30 (0.88-1.92)	.186
Age					
	<43	1.00 (Referent)		1.00 (Referent)	
	43-50	1.10 (0.97-1.25)	.130	1.11 (0.98-1.27)	.100
	51-57	0.93 (0.81-1.06)	.252	1.04 (0.91-1.20)	.578
	>57	1.08 (0.95-1.22)	.228	1.22 (1.08-1.39)	.002
No. of Patients					
	<37	1.00 (Referent)		1.00 (Referent)	
	38-55	0.92 (0.82-1.04)	.184	0.89 (0.79-1.00)	.053
	56-78	0.93 (0.82-1.06)	.297	0.93 (0.81-1.07)	.301
	>78	0.91 (0.79-1.05)	.190	0.95 (0.83-1.10)	.494
Medical School Affiliation					
	Major	1.00 (Referent)		1.00 (Referent)	
	Mixed	1.09 (0.83-1.43)	.532	1.06 (0.80-1.40)	.699
	None	0.90 (0.72-1.13)	.361	1.03 (0.81-1.30)	.814
	Non-Institutional	1.21 (1.02-1.44)	.028	1.41 (1.18-1.70)	.0002

Abbreviations: CI, Confidence Interval; DO, Doctor of Osteopathy; MD, Doctor of Medicine; OR, Odds Ratio; PSA, Prostate Specific Antigen; SEER, Surveillance, Epidemiology, and End Results; USD, United States Dollar

* Comorbidity Index based on a modification of the Charlson Comorbidity Index

** P values calculated from Hierarchical Generalized Linear Mixed Models

Table 6.3 Characteristics of index urologists who diagnosed patients from 2004-2007 with locoregional prostate cancer

			No.	%
All Urologists			2,405	100.0
Age				
	<43		728	30.3
	43-50		561	23.3
	51-57		488	20.3
	>57		628	26.1
Sex				
	Male		2,329	96.8
	Female		76	3.2
Board Certification				
	Yes		2,247	93.4
	No		158	6.6
US Trained				
	Yes		2,030	84.4
	No		375	15.6
Degree Type*				
	MD		2,346	97.6
	DO		59	2.5
Years After Medical School Graduation				
	<16		722	30.0
	16-24		605	25.2
	25-31		443	18.4
	>31		635	26.4
No. of Patients				
	<37		1,455	60.5
	38-55		444	18.5
	56-78		303	12.6
	>78		203	8.4
Medical School Affiliation				
	Major		145	6.0
	Mixed		82	3.4
	None		129	5.4
	Non-Institutional		2,049	85.2

Abbreviations: DO, Doctor of Osteopathy; MD, Doctor of Medicine

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CHAPTER 7 THIRD ESSAY — DETERMINANTS OF THE COMBINED USE OF EXTERNAL BEAM RADIATION THERAPY AND BRACHYTHERAPY FOR LOW-RISK CLINICALLY LOCALIZED PROSTATE CANCER

Introduction

The management of low-risk clinically localized prostate cancer is controversial, and in the absence of high quality randomized control trials[1] to inform best practice, treatment choices are driven by personal beliefs[2] with resultant wide variation in practice patterns[3,4]. There are also growing concerns about prostate cancer overtreatment[4]. Multiple reports indicate increased prevalence of aggressive therapy among low-risk clinically localized prostate cancer patients[2,4-10]. At the same time, patterns of care for prostate cancer patients are also shifting[9,11]. In 1991, 54% of Medicare prostate cancer patients received surgical treatments and 33% received radiation therapy. By 2002, only 24% were treated surgically, whereas 47% received radiation therapy[11]. The increasing utilization of radiation therapy comes with a diverse array of delivery modalities; retrospective studies and non-randomized trials to date, however, suggest that cancer-specific outcomes are similar across treatments for men with low-risk prostate cancer[12-14].

The clinical benefit of combining external beam radiation therapy (EBRT) and brachytherapy (BT) for low-risk clinically localized prostate cancer has yet to be proven[15-17]. In fact, there exist multiple studies that demonstrate increased rates of adverse side effects associated with genitourinary and gastrointestinal toxicity, and reduction in health related quality of life when EBRT is supplemented with BT[18-23]. Consequently, a combination of EBRT with BT for low-risk clinically localized prostate cancer patients is not supported by clinical practice guidelines issued by the American Brachytherapy

Society[24] (ABS), the American Urological Association[25] (AUA) and the National Comprehensive Cancer Network (NCCN)[26-28]. The costs associated with combined therapy are considerably more than for BT as monotherapy[29]. In 2005, mean costs for each Medicare prostate cancer patient ranged from USD26k to USD37k for combined therapy compared to USD17k for BT alone[29]. Current costs of intensity modulated radiation therapy, the most common form of EBRT, have approached USD50k per patient[30], whereas BT costs have remained around USD17k[31]. Despite these differences in cost, there remains a persistent trend of patients with low-risk clinically localized prostate cancer receiving combined EBRT and BT[9,10,32,33]. This may be a reflection of socioeconomic and geographic variation as indicated in previous studies[34-36] or may be associated with practice site[2] and physician characteristics[37].

By using clinical guidelines issued by the ABS, AUA and the NCCN, this study investigates the determinants of the combined use of EBRT and BT for low-risk, clinically localized prostate cancer patients; a specific case of guideline discordant care. I investigated the association of patient and radiation oncologist characteristics on the patient's receipt of combined therapy.

Methods

Data Sources

The Surveillance, Epidemiology and End Results (SEER)-Medicare database, which links cancer registry information in selected geographic areas of the U.S. with claims for covered health care services of Medicare beneficiaries[38], is used to create my analytical cohort using the criteria in Figure 7.1. During the study period, incident cancer cases are available from 16 SEER registries from 2004 through 2007. Data from the Louisiana SEER registry is not used in this study due to missing 2005 data following Hurricane Katrina. Data from metropolitan Atlanta and Rural Georgia SEER registries are hereinafter classified as Georgia.

Characteristics of physicians who treated the SEER-Medicare patients are obtained from the American Medical Association (AMA) Physician Masterfile.

Institutional Review Board approval was obtained from Morehouse School of Medicine and Emory University.

Patient Characteristics

Patient characteristics used in this study are presented in Table 7.1. Clinical characteristics that correspond to low prostate cancer recurrence risk as defined by NCCN[27,28], specifically, prostate-specific antigen (PSA) level < 10 ng/mL at time of diagnosis, clinical stage T1-T2a and low-intermediate tumor grade (low, Gleason grade 2-4; intermediate, Gleason grade 2 – 6)[39,40], are extracted from SEER files. In addition, race, ethnicity, age, marital status, rural status, SEER region of residence at the time of diagnosis and year of diagnosis are determined from SEER files. Education and income levels are based on US Census tract data from 2000; with categories chosen to ensure a

reasonable distribution with cutoffs approximately corresponding to quartiles. A modified Charlson comorbidity index from Medicare Part A and Part B claims[41,42] is calculated for each patient using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes consistent with comorbidities of interest. Claims are examined from one year before to one month after cancer diagnosis for eligible codes.

Patients who received radical prostatectomy or bilateral orchiectomy (defined elsewhere[43]) are removed from the study cohort. Thus, my intent is to create a relatively homogenous sample of patients with low-risk clinically localized prostate cancer who would not be candidates for combined EBRT and BT, according to ABS, AUA and the NCCN guidelines.

To assign a principal radiation oncologist to each patient, criteria are adapted from Shahinian et al.[37]. Patients who did not see at least one radiation oncologist in the year after diagnosis on at least 2 separate days are excluded. If a patient saw two or more radiation oncologists, he is assigned to the radiation oncologist who saw him for at least 75% of his radiation oncologist visits in the year after diagnosis. If no single radiation oncologist accounted for at least 75% of all radiation oncologist visits associated with that patient, he is excluded.

Radiation Oncologist Characteristics

Radiation oncologists who treated prostate cancer are identified using either the Health Care Financing Administration specialty codes in Medicare claims, the physician specialty (primary or secondary) information from the AMA Physician Masterfile or the radiation oncologist board certification identified through the ABMS information within the AMA Physician Masterfile. Other radiation oncologist characteristics obtained from the AMA Physician Masterfile included, age, gender, years after medical school graduation,

location of training (US or otherwise), type of degree [Doctor of Medicine (MD) or Doctor of Osteopathy (DO)] and radiation oncology board certification (Table 7.1). Radiation oncologists' patient volume is defined as the number of unique prostate cancer Medicare patients that each radiation oncologist saw during the study period. The categories chosen for the radiation oncologists' patient volume, age, and years after medical school graduation are pre-specified to ensure a reasonable distribution with cutoffs approximately corresponding to quartiles.

Radiation Oncologists Medical School Affiliation

The source files for key variables used to categorize the radiation oncologist medical school affiliation are summarized in Figure 3.3 in Chapter 3. Radiation oncologists' medical school affiliations are derived from the SEER-Medicare Hospital (HOSP) file and adapted from methods previously described elsewhere[37,44]. Radiation oncologists are categorized as having a *major* medical school affiliation if all their inpatient [from the Medicare Provider Analysis and Review (MEDPAR) file] and institutional outpatient [from the Medicare Outpatient Standard Analytical File (OUTSAF)] claims during the study period are submitted from hospitals with a major medical school affiliation (as defined within the HOSP file). Conversely, radiation oncologists are categorized as having *no* medical school affiliation if all of their inpatient and institutional outpatient claims are from hospitals with no medical school affiliation. Since claims from the MEDPAR file do not contain Unique Physician Identifier Numbers (UPIN), MEDPAR claims are assigned UPINs associated with National Claims History (NCH) file claims (consisting of mostly non-institutional physician/ supplier claims) if 1) the patient associated with both types of claims matched, 2) the place of service of the NCH claim was institutional[45] and 3) the NCH claims dates fell between the MEDPAR admission and discharge dates. Radiation oncologists whose claims can only be found in the NCH file and whose claims cannot be

matched with the MEDPAR file (as described previously) are categorized as having a *non-institutional* affiliation. All other radiation oncologists are categorized as having a *mixed* medical school affiliation.

Measurement of Treatment and Outcomes

EBRT and BT are identified from Medicare's MEDPAR, OUTSAF and NCH files based on the presence of Current Procedural Terminology, fourth edition codes and ICD-9-CM codes defined elsewhere[29,46]. The primary outcome is the receipt of combined EBRT and BT in the first six months after low-risk clinically localized prostate cancer diagnosis. Therefore, this study is limited to investigating if combined radiation therapy was used as a form of initial therapy among low-risk clinically localized prostate cancer patients. In cases where combined EBRT and BT are observed, they are not supported by clinical evidence and represent discordance with major clinical practice guidelines[24-28].

Statistical Analyses

Differences in the proportion of patients receiving combined radiation therapy across radiation oncologist and patient characteristics are evaluated using χ^2 tests. The effect of patient and radiation oncologist characteristics on receipt of combined radiation therapy is evaluated using logistic hierarchical generalized linear mixed models[47] (GLMM) and estimated using the restricted pseudo-likelihood methodology[47-49]. Hierarchical GLMMs account for the clustering of the receipt of combined radiation therapy among patients who have the same radiation oncologist. The unit of analysis is the patient. The radiation oncologist associated with each patient is used as the clustering variable. Univariate and adjusted multivariate odds ratios (ORs) and 95% confidence intervals (CIs) for receipt of combined radiation therapy are estimated for the radiation oncologist and patient variables listed in Table 7.2. Mean predicted probabilities of the receipt of combined radiation therapy across different SEER regions stratified by medical school affiliation of the radiation oncologists are also estimated from the final fitted model (Figure 7.2).

In order to estimate the percentage of total variance in the combined use of EBRT and BT attributable to the radiation oncologist, the intraclass correlation coefficient (ICC) from hierarchical GLMM using the threshold method[50] is estimated. Both a null model, excluding patient and radiation oncologist characteristics, and adjusted models, which include all these characteristics, are constructed. From the adjusted models, the residual ICC, representing the percentage of variance attributable to the radiation oncologist after adjustments, is calculated. All statistical testing is two-sided, performed at the 5% significance level, and used SAS version 9.3 (SAS Institute, Cary, NC).

Results

A total of 5,531 patients in the SEER-Medicare database were diagnosed with incident low-risk clinically localized prostate cancer from 2004 through 2007 and assessed as meeting the eligibility criteria defined in Figure 7.1. A total of 708 principal radiation oncologists treated these patients. Radiation oncologists are predominantly male (85.0%), board certified (72.2%), trained in the United States (84.0%), and had a patient volume of less than 13 (68.9%) throughout the study period (Table 7.3).

Table 7.1 compares the percentages of patients who received combined radiation therapy classified by their sociodemographic, clinical and principal radiation oncologist characteristics. Overall, 6.4% of the low-risk clinically localized prostate cancer patients were treated with combined EBRT and BT. Combined radiation therapy was more commonly administered to patients who resided in Georgia and in census tracts with median income greater than USD 52,000. The principal radiation oncologists associated with patients who received combined radiation therapy were more likely to be practicing in non-institutional settings, to be MDs and/or to have a patient volume size between 13 and 27.

By using logistic hierarchical GLMM analyses, I investigated the determinants of receipt of combined radiation therapy (Table 7.2), while controlling for the fact that multiple patients may be treated by the same principal radiation oncologist. As the unadjusted odds ratios show, combined radiation therapy is significantly associated with patient's SEER region of residence, patient's non-marital status and the non-institutional practice affiliation of the patient's principal radiation oncologist.

After adjusting for known potential patient and radiation oncologist characteristics, significant regional variations remain. In particular, patients who reside in the SEER

region of Georgia are significantly more likely to receive combined radiation therapy compared to all other SEER regions; for example, the odds of receiving combined therapy for patients residing in Georgia (OR, 1.0; referent) is approximately 20 times that of patients residing in California (OR, 0.05; 95% CI, 0.03-0.11, p<0.0001). In addition, patients who reside in census tracts with median income between USD 52,000 and USD 70,999 are significantly more likely to receive combined radiation therapy (OR, 1.70; 95% CI, 1.01-2.85, p=0.046) when compared to those residing in census tracts with median income less than USD 39,000. Non-Hispanic Black patients are significantly less likely to receive combined radiation therapy (OR, 0.62; 95% CI, 0.40-0.96, p=0.031) when compared to non-Hispanic White patients.

To further investigate the effects of geographic variation on the receipt of combined radiation therapy, the predicted probabilities from the logistic hierarchical GLMM are estimated. When analyzing across the categories of patients' principal radiation oncologists' medical school affiliation, the mean predicted probabilities of receiving combined radiation therapy for patients residing in Georgia are the highest compared to all other SEER regions; in particular, Georgia patients who consult radiation oncologists with a non-institutional affiliation have the highest probability (46.4%) of receiving combined radiation therapy (Figure 7.2). Conversely, the mean predicted probabilities of receiving combined radiation therapy for patients residing in Utah are the lowest across all categories of principal radiation oncologists' medical school affiliation, when compared to all other SEER regions (Figure 7.2).

As a measure of the overall influence of the radiation oncologist on the patient's receipt of combined radiation therapy, I estimated the ICC. In the null model, with no predictors included, it is assumed that the probability of the receipt of combined radiation therapy does not vary by individual patient or radiation oncologist characteristics. From the null

model, I estimate that 42.4% of the variance in receiving combined radiation therapy can be attributed to the radiation oncologist. After adjusting for patient and radiation oncologist characteristics listed in Table 7.2, the variance attributable to the radiation oncologist decreases to 36.6%.

Discussion

After the adjustment for other patient and radiation oncologist characteristics, the hierarchical multivariable analysis suggests important regional differences in the utilization of combined radiation therapy on low-risk clinically localized prostate cancer. This treatment regimen is not consistent with patient-centered clinical guidelines, is more costly than monotherapy, is considered unlikely to have significant survival benefit and has been shown to result in increased radiation related toxicities in several studies. My findings are consistent with, and complement, those from prior studies that observed variation in treatment selection across SEER regions with a more generalized prostate cancer population [9,51]; one previous study found significant increased odds of receiving BT with or without EBRT in Atlanta (OR, 13.8; 95% CI, 2.9-64.7) when compared to California among patients with clinically localized prostate cancer[9]. Such geographic variations in treatment patterns observed may reflect local practice patterns[52].

Several studies have documented lower rates of overall radiation[51,53,54] and BT[55-57] in Black men compared to White men. My study demonstrates that this disparity may have led to increased concordance with clinical guidelines that recommend radiation monotherapy (i.e. either BT or EBRT) for low-risk clinically localized prostate cancer. Similarly, the significant income effects that are also observed in a different study[51] may have been adversely related to the increased odds of receiving combined radiation therapy.

Clinical guidelines from the ABS[24] (published in 1999) and the NCCN[26-28,58] (published annually since 2000) have, throughout the study period, consistently recommended radiation monotherapy for low-risk clinically localized prostate cancer. However in 1995, the AUA published no specific recommendations about the use of combined radiation

therapy[59]. This may have potentially influenced radiation oncologists' behavior regarding the use of combined therapy on patients. Nonetheless, in 2007 the AUA did specifically recommend monotherapy for low-risk clinically localized prostate cancer [25]. Although, my results generally support findings from other studies indicating that higher quality of care and better guideline compliance may be offered in academic settings versus non-academic settings[60-63], the lack of adherence to clinical guidelines may also be the consequence of other barriers that are not directly controlled for in this study[64].

I acknowledge important limitations of my SEER-Medicare based study[38]. Patterns of radiation therapy use among the elderly may not be generalizable to other patient population (e.g. younger, privately insured patients and/or those receiving care in health maintenance organizations) and may not be representative of the radiation oncologist's entire practice. Nonetheless, approximately 79% of men with incident prostate cancer are 65 years or older[65] and in 2003, 89% of Medicare beneficiaries are covered under the traditional fee-for-service program[66]. Individual patient selection biases not assessed in this study may have led to variability in the observations. It is unclear if my study results reflect decisions of radiation oncologists or individual choices made by patients. Previous analyses of the major role physicians play in advising and influencing prostate cancer patients regarding best treatment options[67-72] suggest that patient preference is unlikely to entirely explain the observed radiation oncologist treatment patterns.

While patient and clinical factors influence treatment decisions, there is growing evidence that physician characteristics are also important determinants of cancer care[37,73-77]. To my knowledge, this is the first study to explore patient and physician related determinants of guideline discordant care for low-risk clinically localized prostate cancer. Previous studies examining variance in treatment attributable to different oncology physician specialties have found ICCs to be lower (i.e. 21% - 23%)[76,78] than in

my study. One interpretation of my findings is that changing radiation oncologist behavior would likely lead to a larger impact on clinical practice patterns[79,80] for low-risk clinically localized prostate cancer patients. While the adjusted hierarchical GLMM yielded non-significant associations for all the radiation oncologist characteristics used in this study, future research is needed to explore other radiation oncologist characteristics (e.g. intrinsic motivation, professionalism) that may account for treatment variation.

The reasons behind the eventual decision to undergo combined radiation therapy are likely to be complex and multifactorial[81-84]. A prior study found that radiation therapy facilities with ownership interests by non-radiation oncologists performed 58% more procedures than did facilities without ownership conflicts[85]. Additional research is needed to investigate whether the substantially higher probability of discordance by radiation oncologists practicing in non-institutional settings may be associated with the potential for self-referral among urology-radiation oncology integrated practices. Prior literature has suggested the potential for overtreatment of prostate cancer patients[30,86,87].

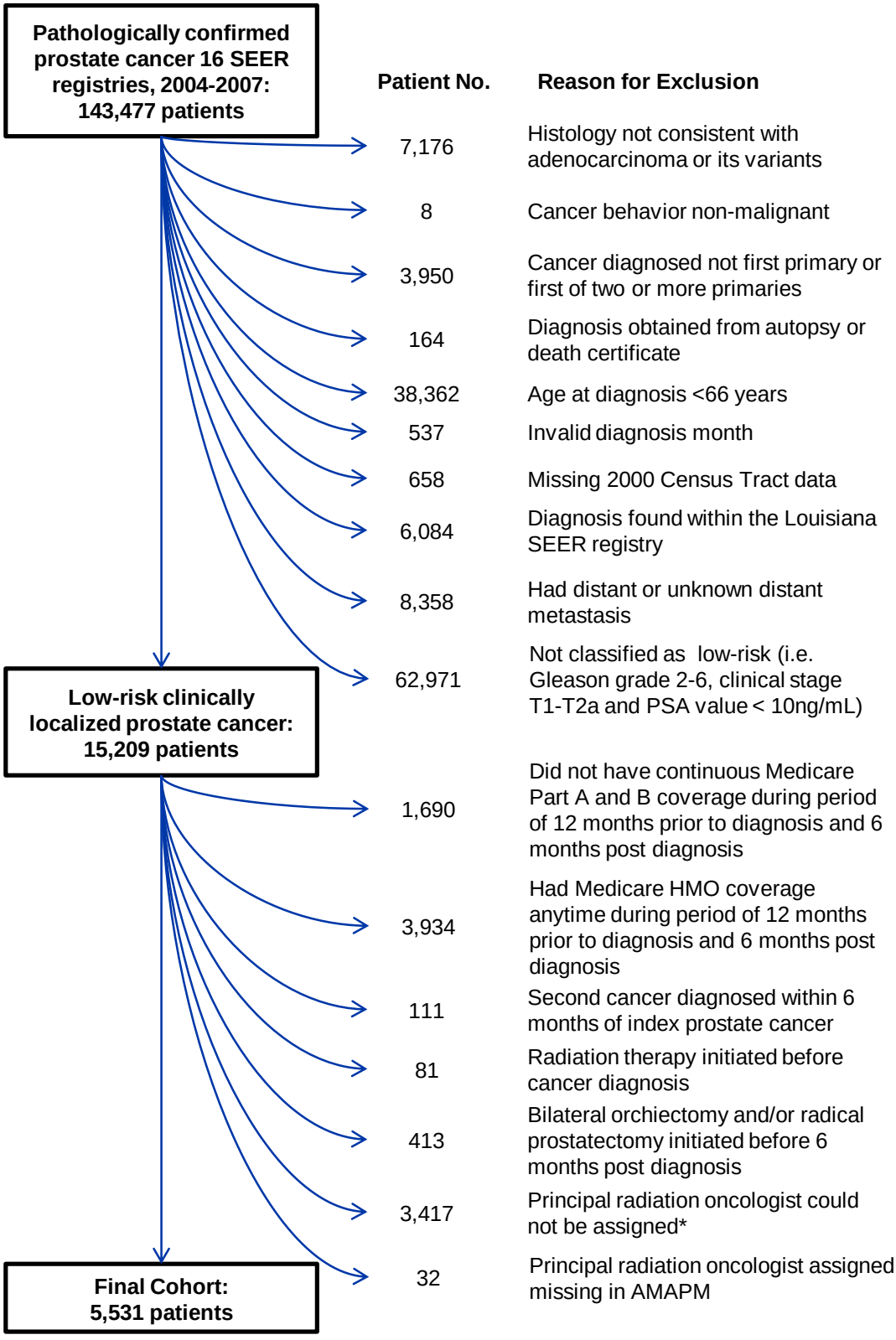

Figure 7.1 Definition of study cohort of 5,531 men with low-risk clinically localized prostate cancer. HMO, Health Maintenance Organization; SEER, Surveillance, Epidemiology and End Results; AMAPM, American Medical Association Physician Masterfile; PSA, Prostate Specific Antigen level at diagnosis; *Resulting from adaption of criteria developed by Shahinian et al.[38]

Table 7.1 Percentage of patients receiving combined radiation therapy within 6 months after prostate cancer diagnosis according to their clinical and sociodemographic characteristics, and the characteristics of their radiation oncologists

		No.	% of patients receiving combined radiation therapy	P**
All patients		5,531	6.4	
Patient Sociodemographic Characteristics				
Age at Diagnosis				.227
	66-69	1,744	6.5	
	70-74	2,201	6.5	
	75-79	1,267	6.9	
	80-84	283	4.2	
	≥85	36	5.6	
Race/ Ethnicity				.259
	Non-Hispanic White	4,453	6.1	
	Non-Hispanic Black	422	7.6	
	Hispanic	356	8.7	
	Non-Hispanic Asian/ Pacific Islander	216	7.4	
	Other/ Unknown	84	7.1	
Marital Status				.155
	Married	4,211	6.7	
	Not Married	986	5.1	
	Unknown	334	6.6	
SEER Region of Residence				<.0001
	Georgia	246	33.7	
	California	1,684	3.6	
	Connecticut	506	2.6	
	Detroit	419	6.2	
	Hawaii	96	3.1	
	Iowa	221	6.8	
	Kentucky	492	5.1	
	New Jersey	1,323	8.7	
	New Mexico	81	6.2	
	Seattle	320	2.8	
	Utah	143	0.7	
Rural Status				.625
	Non-Rural	5,454	6.4	
	Rural	77	7.8	
Census Tract: Percentage of Adults with Less than High School Education				.067
	<7.4	1,398	6.9	
	7.4 - <12.70	1,361	6.5	
	12.70 - <21.10	1,383	5.0	
	≥21.10	1,389	7.3	
Census Tract: Median Income (USD)				.038
	<39,000	1,384	5.6	
	39,000 - <52,000	1,371	5.3	
	52,000 - <71,000	1,405	7.4	
	≥71,000	1,371	7.4	

Table 7.1 Percentage of patients receiving combined radiation therapy within 6 months after prostate cancer diagnosis according to their clinical and sociodemographic characteristics, and the characteristics of their radiation oncologists (continued)

		No.	% of patients receiving combined radiation therapy	P**
Patient Clinical Characteristics				
Comorbidity Index*				.377
	0	3,538	6.0	
	1	1,376	6.8	
	2	382	7.9	
	≥3	235	7.7	
Clinical Tumor Stage				.083
	T1	4,840	6.7	
	T2a	691	4.9	
Tumor Grade				.130
	Low	60	1.7	
	Intermediate	5,471	6.5	
Year of Diagnosis				
	2004	1,419	6.4	.227
	2005	1,338	5.3	
	2006	1,455	6.9	
	2007	1,319	7.1	

Table 7.1 Percentage of patients receiving combined radiation therapy within 6 months after prostate cancer diagnosis according to their clinical and sociodemographic characteristics, and the characteristics of their radiation oncologists (continued)

		No.	% of patients receiving combined radiation therapy	P**
Radiation Oncologist Characteristics				
Age				.905
	<41	1,372	6.7	
	41-46	1,596	6.1	
	47-52	1,304	6.3	
	>52	1,259	6.7	
Sex				.343
	Male	5,163	6.4	
	Female	368	7.6	
Board Certification				.060
	Yes	4,019	6.8	
	No	1,512	5.4	
US Trained				.520
	Yes	4,769	6.5	
	No	762	5.9	
Degree Type				.041
	MD	5,443	6.5	
	DO	88	1.1	
Years after medical school graduation				.246
	<13	1,299	6.5	
	14-18	1,586	7.2	
	19-24	1,369	6.6	
	>24	1,277	5.3	
No. of patients				.043
	<13	1,343	6.0	
	13-27	1,453	7.9	
	28-48	1,433	5.4	
	>48	1,302	6.4	
Medical School Affiliation				<.0001
	Major	766	4.3	
	Mixed	2,835	5.0	
	None	1,665	8.6	
	Non-Institutional	265	14.7	

Abbreviations: DO, Doctor of Osteopathy; MD, Doctor of Medicine; SEER, Surveillance, Epidemiology, and End Results; USD, United States Dollar

* Comorbidity Index based on a modification of the Charlson Comorbidity Index

** P values calculated from two-sided χ^2 tests for heterogeneity in proportion of patients receiving combined radiation therapy across different patient sociodemographic, clinical characteristics and their radiation oncologists' characteristics

Table 7.2 Unadjusted univariate and adjusted multivariate multilevel regression models predicting the odds of receiving combined radiation therapy among clinically localized low-risk prostate cancer patients

Characteristics		Unadjusted OR (95% CI)	P**	Adjusted OR (95% CI)	P**
Patient Sociodemographic Characteristics					
Age at Diagnosis					
	66-69	1.00 (Referent)		1.00 (Referent)	
	70-74	1.00 (0.77-1.29)	.972	0.99 (0.76-1.27)	.906
	75-79	1.06 (0.80-1.42)	.674	1.00 (0.72-1.38)	.989
	80-84	0.64 (0.35-1.18)	.150	0.56 (0.31-1.00)	.052
	≥85	0.85 (0.20-3.58)	.824	0.73 (0.26-2.09)	.559
Race/ Ethnicity					
	Non-Hispanic White	1.00 (Referent)		1.00 (Referent)	
	Non-Hispanic Black	0.74 (0.48-1.15)	.178	0.62 (0.40-0.96)	.031
	Hispanic	1.29 (0.86-1.94)	.226	1.50 (0.95-2.36)	.084
	Non-Hispanic Asian/ Pacific Islander	1.68 (0.67-4.20)	.267	2.39 (0.87-6.56)	.090
	Other/ Unknown	0.71 (0.25-2.03)	.520	0.72 (0.23-2.29)	.582
Marital Status					
	Married	1.00 (Referent)		1.00 (Referent)	
	Not Married	0.72 (0.53-0.98)	.035	0.76 (0.55-1.05)	.090
	Unknown	1.05 (0.62-1.76)	.869	1.01 (0.55-1.85)	.976
SEER Region of Residence					
	Georgia	1.00 (Referent)		1.00 (Referent)	
	California	0.07 (0.03-0.14)	<.0001	0.05 (0.03-0.11)	<.0001
	Connecticut	0.05 (0.02-0.12)	<.0001	0.05 (0.02-0.12)	<.0001
	Detroit	0.12 (0.05-0.32)	<.0001	0.13 (0.04-0.36)	.0001
	Hawaii	0.04 (0.01-0.17)	<.0001	0.02 (0.002-0.16)	.0003
	Iowa	0.12 (0.05-0.30)	<.0001	0.12 (0.05-0.32)	<.0001
	Kentucky	0.14 (0.06-0.33)	<.0001	0.13 (0.05-0.33)	<.0001
	New Jersey	0.11 (0.05-0.25)	<.0001	0.11 (0.05-0.25)	<.0001
	New Mexico	0.16 (0.05-0.49)	.001	0.18 (0.05-0.63)	.007
	Seattle	0.07 (0.03-0.20)	<.0001	0.07 (0.03-0.20)	<.0001
	Utah	0.02 (0.002-0.29)	.004	0.03 (0.002-0.38)	.008
Rural Status					
	Non-Rural	1.00 (Referent)		1.00 (Referent)	
	Rural	1.46 (0.68-3.15)	.335	1.38 (0.60-3.16)	.449
Census Tract: Percentage of Adults with Less than High School Education					
	<7.4	1.00 (Referent)		1.00 (Referent)	
	7.4 - <12.70	0.91 (0.60-1.38)	.649	0.94 (0.56-1.57)	.807
	12.70 - <21.10	0.73 (0.50-1.08)	.117	0.81 (0.48-1.35)	.415
	≥21.10	0.94 (0.66-1.34)	.714	1.20 (0.64-2.25)	.564
Census Tract: Median Income (USD)					
	<39,000	1.00 (Referent)		1.00 (Referent)	
	39,000 - <52,000	0.87 (0.60-1.26)	.453	1.02 (0.67-1.55)	.930
	52,000 - <71,000	1.34 (0.93-1.93)	.114	1.70 (1.01-2.85)	.046
	≥71,000	1.12 (0.76-1.67)	.563	1.37 (0.26-2.09)	.377

Table 7.2 Unadjusted univariate and adjusted multivariate multilevel regression models predicting the odds of receiving combined radiation therapy among clinically localized low-risk prostate cancer patients (continued)

		Unadjusted		Adjusted	
Characteristics		**OR (95% CI)**	**P****	**OR (95% CI)**	**P****
Patient Clinical Characteristics					
Comorbidity Index*					
	0	1.00 (Referent)		1.00 (Referent)	
	1	1.08 (0.83-1.41)	.553	1.16 (0.88-1.53)	.284
	2	1.34 (0.85-2.12)	.209	1.32 (0.81-2.13)	.266
	≥3	1.33 (0.72-2.44)	.364	1.45 (0.77-2.72)	.250
Clinical Tumor Stage					
	T1	1.00 (Referent)		1.00 (Referent)	
	T2a	0.86 (0.58-1.26)	.440	0.98 (0.67-1.44)	.924
Tumor Grade					
	Low	1.00 (Referent)		1.00 (Referent)	
	Intermediate	3.33 (0.47-23.42)	.226	3.09 (0.40-23.68)	.279
Year of Diagnosis					
	2004	1.00 (Referent)		1.00 (Referent)	
	2005	0.79 (0.56-1.12)	.190	0.81 (0.56-1.17)	.258
	2006	0.98 (0.68-1.41)	.916	0.93 (0.64-1.36)	.710
	2007	0.94 (0.66-1.34)	.735	0.88 (0.61-1.26)	.482

Table 7.2 Unadjusted univariate and adjusted multivariate multilevel regression models predicting the odds of receiving combined radiation therapy among clinically localized low-risk prostate cancer patients (continued)

Characteristics		Unadjusted OR (95% CI)	P**	Adjusted OR (95% CI)	P**
Radiation Oncologist Characteristics					
Sex					
	Male	1.00 (Referent)		1.00 (Referent)	
	Female	1.56 (0.89-2.71)	.118	1.46 (0.82-2.63)	.203
Board Certification					
	Yes	1.00 (Referent)		1.00 (Referent)	
	No	0.95 (0.60-1.50)	.817	1.30 (0.70-2.42)	.413
US Trained					
	Yes	1.00 (Referent)		1.00 (Referent)	
	No	0.95 (0.57-1.58)	.834	1.06 (0.58-1.94)	.840
Degree Type					
	MD	1.00 (Referent)		1.00 (Referent)	
	DO	0.41 (0.02-7.05)	.537	0.18 (0.01-6.58)	.350
Years after Medical School Graduation					
	<13	1.00 (Referent)		1.00 (Referent)	
	14-18	0.81 (0.44-1.47)	.482	0.75 (0.43-1.31)	.309
	19-24	0.80 (0.44-1.47)	.479	0.91 (0.51-1.64)	.759
	>24	0.80 (0.44-1.43)	.443	0.72 (0.33-1.61)	.429
No. of Patients					
	<13	1.00 (Referent)		1.00 (Referent)	
	13-27	1.03 (0.64-1.64)	.911	1.29 (0.80-2.08)	.302
	28-48	0.67 (0.37-1.20)	.174	1.02 (0.52-1.98)	.959
	>48	0.73 (0.30-1.81)	.500	0.82 (0.38-1.77)	.614
Medical School Affiliation					
	Major	1.00 (Referent)		1.00 (Referent)	
	Mixed	1.10 (0.59-2.06)	.768	1.04 (0.54-2.02)	.911
	None	1.61 (0.85-3.05)	.143	1.26 (0.62-2.57)	.518
	Non-Institutional	2.79 (1.19-6.55)	.019	1.68 (0.68-4.16)	.260

Abbreviations: CI, Confidence Interval; DO, Doctor of Osteopathy; MD, Doctor of Medicine; OR, Odds Ratio; SEER, Surveillance, Epidemiology, and End Results; USD, United States Dollar

* Comorbidity Index based on a modification of the Charlson Comorbidity Index

** P values calculated from Hierarchical Generalized Linear Mixed Models

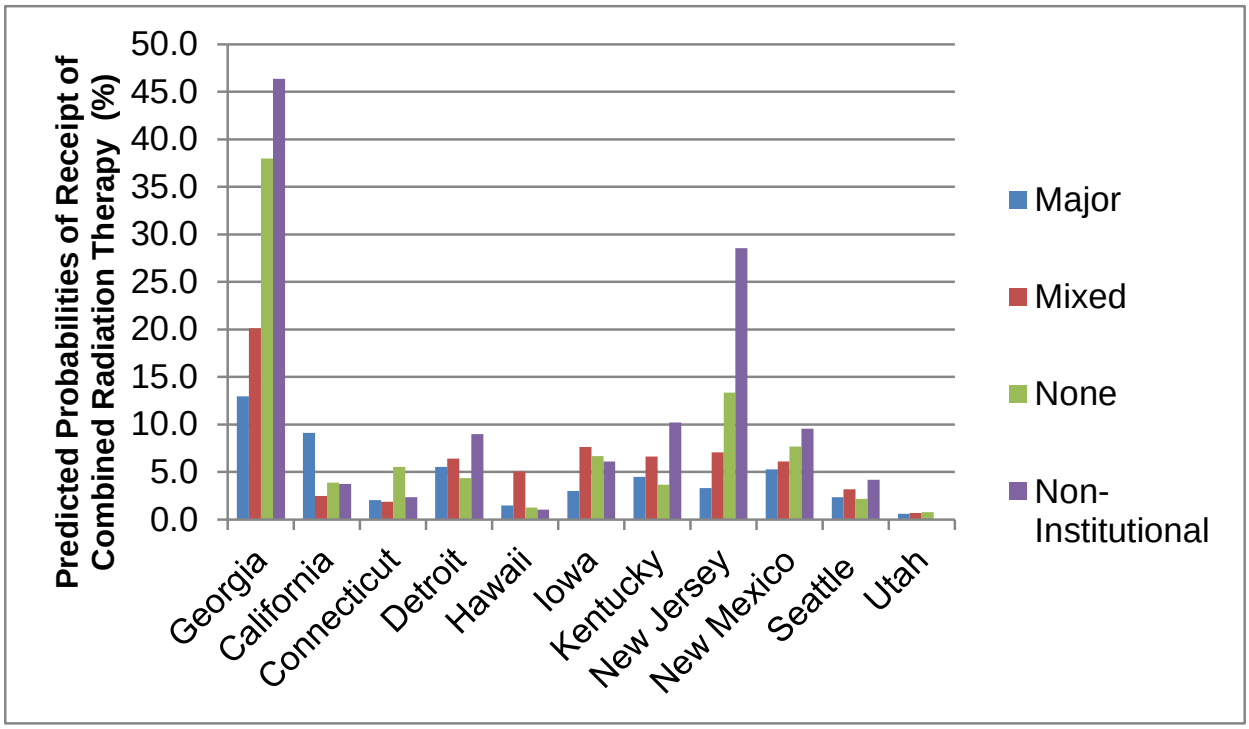

Figure 7.2 Predicted probabilities of patient receipt of combined radiation therapy for all SEER regions, adjusted for patient sociodemographic and clinical characteristics and their principal radiation oncologists' characteristics, are estimated from hierarchical generalized mixed models for each category of principal radiation oncologists' medical school affiliation; SEER, Surveillance, Epidemiology and End Results; Probability of the receipt of combined therapy for Utah patients treated by radiation oncologists with a non-institutional affiliation cannot be estimated as the original sample did not contain any patient in that category.

Table 7.3 Characteristics of principal radiation oncologists who treated patients diagnosed from 2004-2007 with clinically localized low-risk prostate cancer

		No.	%
All Radiation Oncologists		708	100.0
Age			
	<41	211	29.8
	41-46	176	24.9
	47-52	151	21.3
	>52	170	24.0
Sex			
	Male	602	85.0
	Female	106	15.0
Board Certification			
	Yes	511	72.2
	No	197	27.8
US Trained			
	Yes	595	84.0
	No	113	16.0
Years after Medical School Graduation			
	<13	202	28.5
	14-18	179	25.3
	19-24	141	19.9
	>24	186	26.3
No. of Patients			
	<13	488	68.9
	13-27	130	18.4
	28-48	58	8.2
	>48	32	4.5
Medical School Affiliation			
	Major	122	17.2
	Mixed	263	37.2
	None	235	33.2
	Non-Institutional	88	12.4

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CHAPTER 8 CONCLUSIONS, POLICY IMPLICATIONS AND FUTURE RESEARCH

Conclusions

My study demonstrates that the variability in referral patterns and discordance with major prostate cancer patient-centered clinical treatment guidelines can be attributable to both patient and physician characteristics. In particular the following conclusions can be made regarding the hypotheses (stated in Chapter 2) of the first essay tested in this dissertation.

Conclusion Regarding First Essay Hypothesis 1

Urologists without major medical school affiliations (i.e. urologists with mixed or no medical school affiliation) are significantly more likely than those with major medical school affiliations to utilize guideline discordant ADT on prostate cancer patients. Due to the small sample size of patients treated by non-institutional affiliated urologists, I am unable to draw firm conclusions regarding their ADT treatment patterns.

Conclusion Regarding First Essay Hypothesis 2

ADT reimbursement reductions following the passage of the MMA weakened the positive relationship between urologists without major medical school affiliation and guideline discordant ADT use on prostate cancer patients.

The following conclusion can be made regarding the hypothesis (stated in Chapter 2) of the second essay tested in this dissertation.

Conclusion Regarding Second Essay Hypothesis 1

Locoregional prostate cancer patients diagnosed by major medical school affiliated urologists (compared to patients diagnosed by non-institutional affiliated urologists) are

significantly less likely to subsequently consult radiation oncologists. Urologists with mixed or no medical school affiliation appeared to have similar referral patterns with major medical school affiliated urologists.

The following conclusion can be made regarding the hypothesis (stated in Chapter 2) of the third essay tested in this dissertation.

Conclusion Regarding Third Essay Hypothesis 1

Radiation oncologists with major medical school affiliations are less likely than those without major medical school affiliations to utilize combined EBRT and BT on clinically localized low-risk prostate cancer patients. Although, statistical significance of the associations was not achieved, the effect sizes (measured through the odds ratios) obtained for the different categories of radiation oncologists' medical school affiliations are in line with my expectations.

Specific background and discussions surrounding the dissertation conclusions mentioned above for the first, second and third essays can be found in Chapters 5, 6 and 7 respectively.

Policy Implications and Future Research

Although patient-related factors affected observed treatment and referral patterns, physician characteristics (including their medical school affiliation) exerted substantial influence on the outcomes analyzed in this dissertation. The significant differences in prostate cancer treatment and referral patterns as a function of physician characteristics are cause for concern.

Regulatory changes as well as limitations on reimbursement may drive more rational, evidence-based and patient-centered treatment of prostate cancer patients. However, further interventions to encourage guideline-based treatment of prostate cancer and reduce geographic variation are needed. For example, the US Food and Drug Administration risk evaluation and mitigation strategy (REMS) program[1], which is intended to assess the risks of side effects and other toxicities of drugs and ensure that the benefits outweigh the risks for patients, could be adapted and adopted for ADT and radiation therapy for prostate cancer patients.

The significant associations noted in this study between physician medical school affiliation and prostate cancer treatment/ referral patterns provide insight into what efforts may be successful for improving clinical practice guideline concordance. The effects of medical school affiliation suggest that physician education and retraining should be a priority especially among physicians without medical school affiliation. The distinctive social missions (e.g. education, research, clinical innovation, and caring for disadvantaged patients) of medical school affiliated health care settings may have reduced financial motivations and led to better guideline concordance among medical school affiliated physicians. Nevertheless, the constant changes associated with

[1] http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm

ownership and types of health care settings (see Figure 8.1, 8.2 and 8.3) will only serve to increase the challenges associated with targeting specific physician groups to improve guideline concordance.

Current clinical practice guidelines for the management of prostate cancer may not be sufficient. Clinically important information derived from ongoing and future high-quality randomized trials and comparative effectiveness research will serve to reduce barriers to well-informed decision making and improve prostate cancer treatment and referral decisions. In addition, primary care physicians should also carefully recommend specialists for their patients pre and post-diagnosis and assist in treatment modality decision making.

In addition, increase penetration and sophistication of electronic medical record systems may be useful in encouraging best practice/ guideline compliance through automatic electronic physician prompts.

This dissertation adds significantly to the limited investigation of the influence of physician characteristics and medical school affiliation on treatment and referral patterns of prostate cancer patients. To improve the quality of cancer care, further efforts to determine whether the associations found in this dissertation reflect physician education, experience, practice setting, patient characteristics (e.g. insurance type), or other economic incentives are necessary. Capitation in various forms is anticipated to be an effective means of curbing future health care cost growth particularly resulting from unnecessary care. Future research should explore the differences in geographic variation across Medicare Advantage versus Medicare FFS beneficiaries. A recent study has found that capitated Medicare Advantage (versus Medicare FFS) was associated

with lower procedure rates for cardiovascular procedures but substantial geographic variation remained despite reimbursement structure.[2]

For all three essays of this dissertation, a logistic hierarchical GLMM is used. This imposes the classic monotonically increasing sigmoidal-shape distribution on the outcome variable. However, for non-durable goods (e.g. drugs used for ADT), the cumulative proportion of individuals or firms who have ever used a good is less important than the current proportion of potential users utilizing a good. Alternative modeling strategy that allows for non-sigmoidal-shape distributions should be explored[3].

Physician characteristics are just one set of factors that influence quality of care. Patient care can also be influenced by other hospital and system characteristics. Further design and evaluation of health care system improvements to facilitate guideline concordance for patients with prostate cancer is warranted.

[2] JAMA. 2013 Jul 10;310(2):155-62
[3] Health Econ. 2012 Apr;21(4):428-43

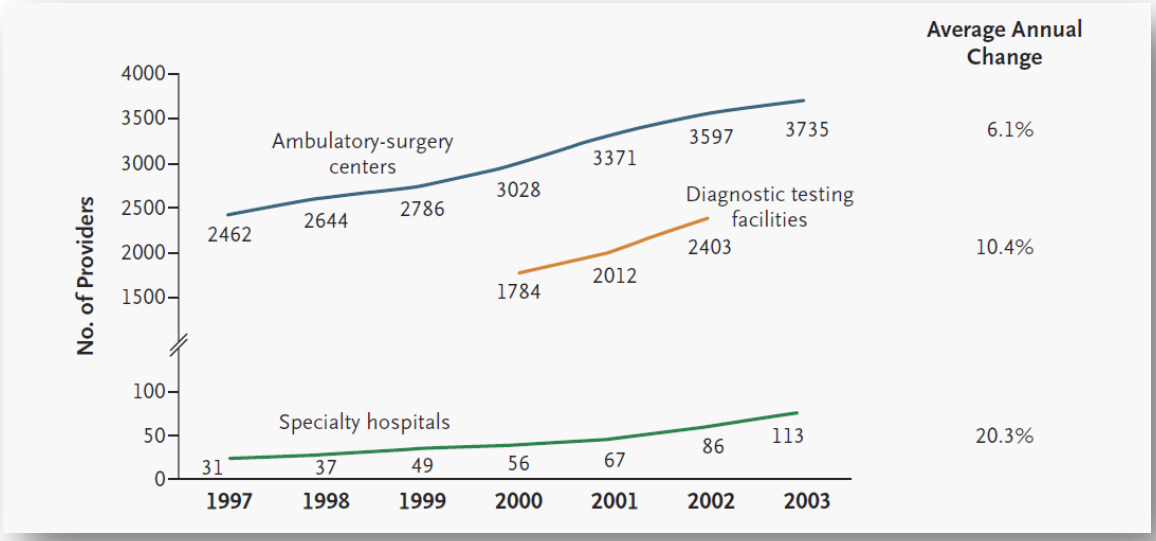

Figure 8.1 Increases in the numbers of ambulatory-surgery centers, diagnostic testing centers, and specialty hospitals from 1997-2003[4]

[4] NEJM 2005;352(1):78-84

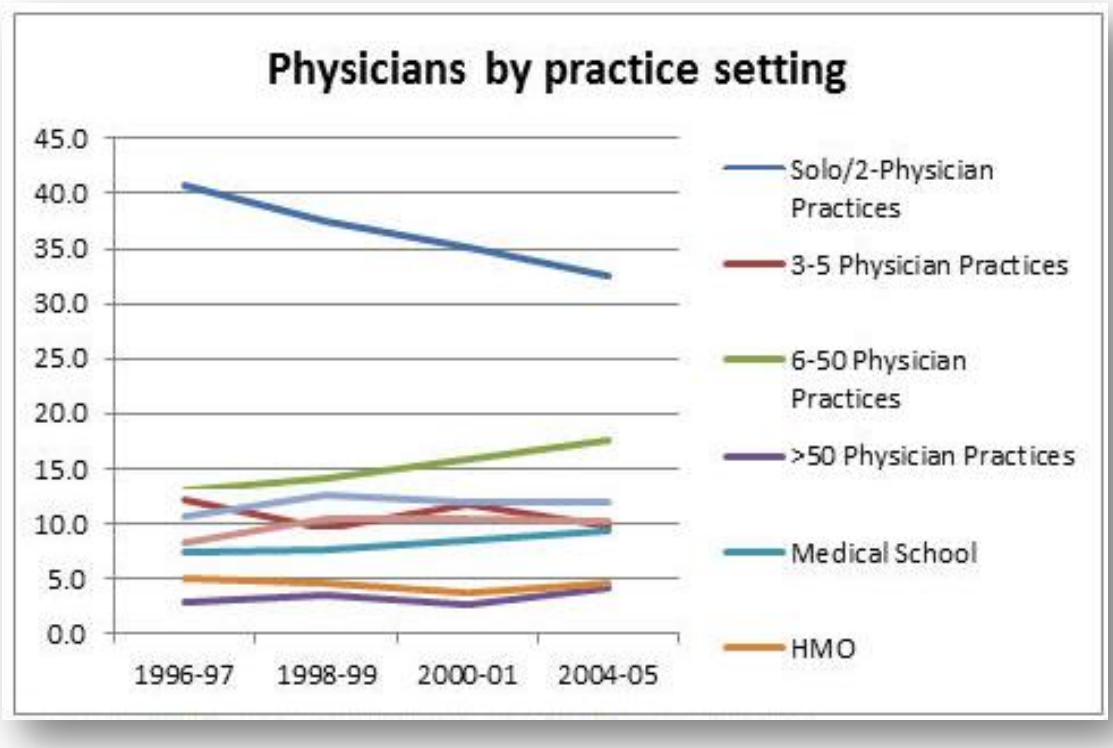

Figure 8.2 Changes in the proportion of physicians practicing in different settings 1996-2005[5]

[5] HSC Community Tracking Study Physician Survey

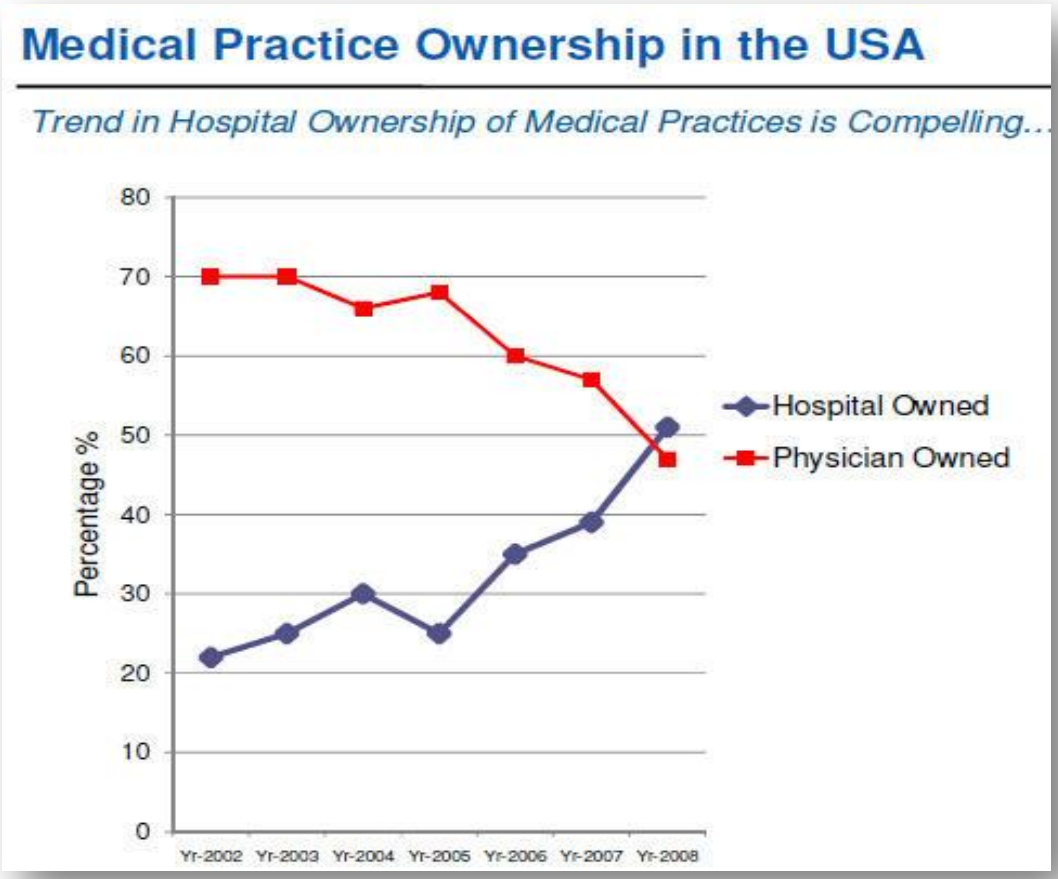

Figure 8.3 Trend in hospital ownership of medical practice 2002-2008[6]

[6] MGMA Physician Compensation and Production Survey