PSA SURVEILLANCE FOLLOWING RADICAL PROSTATECTOMY: WHAT WE KNOW AND WHY IT MATTERS

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ABSTRACT

LAUREL CLAYTON TRANTHAM: PSA Surveillance Following Radical Prostatectomy: What We Know and Why it Matters
(Under the direction of Andrea K. Biddle, PhD)

Disease recurrence is common after initial therapy for prostate cancer, but little is known about how well men receive follow-up surveillance after initial treatment or how patterns of follow-up care may influence choice of initial treatment. The overall objectives of this dissertation were (1): to examine patterns of prostate-specific antigen (PSA) test receipt among elderly men treated with radical prostatectomy for non-metastatic prostate cancer, (2): to validate the radiation therapy variable in Surveillance, Epidemiology, and End Results (SEER) data by comparing treatment receipt with Medicare claims, and (3): to compare through a decision model a “wait and see” approach to radiation therapy in which radiation therapy is initiated only after evidence of disease recurrence to an approach of treating all qualifying men with radiation therapy adjuvant to surgery. This dissertation used population-based SEER-Medicare data to examine the first two aims. The decision model was constructed as a Markov cohort model and populated with data from clinical trials, retrospective studies, surveys, and Medicare fee schedules.

Time from treatment was the dominant factor in predicting whether a man received a PSA surveillance test in a given year following surgery. In all men, test receipt decreased as time from surgery increased. I also found some evidence of racial/ethnic disparities in test receipt as well as evidence that test receipt is influenced by access to care and social support. I found that although there is some disagreement across SEER and Medicare in terms of documentation of adjuvant radiation therapy (ART) receipt, overall agreement is very high. This lends support to previous studies using SEER alone

to study ART. The results from the decision model suggest that most men will benefit more from a wait and see approach to radiation therapy than ART. However, if men do not receive appropriate PSA surveillance testing, ART may be a better option. This research highlights the need for long-term follow-up care plans for men treated with radical prostatectomy for prostate cancer.

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Table of Contents

List of Tables

List of Figures

List of Abbreviations

ADT: Androgen deprivation therapy

AIC: Akaike Information Criterion

AJCC: American Joint Committee on Cancer

ARO: Arbeitsgemeinschaft Radiologische Onkologie (German Cancer Society)

ART: Adjuvant radiation therapy

AUA: American Urological Association

CaP: Prostate cancer

CEAC: Cost-effectiveness acceptability curve

CI: Confidence interval

CPT: Current Procedural Terminology

CT: Computed tomography

DRE: Digital rectal exam

EBRT: External beam radiation therapy

EORTC: European Organisation for Research and Treatment of Cancer

ERS: Economic Research Service

ESRD: End-stage renal disease

FFS: Fee-for-service

GEE: Generalized estimating equations

HCPCS: Healthcare Common Procedure Coding System

HMO: Health maintenance organization

ICD-9: International Classification of Diseases, 9^{th} Revision

ICER: Incremental cost-effectiveness ratio

IMRT: Intensity-modulated radiation therapy

INB: Incremental net benefit

ISPOR: International Society for Pharmacoeconomics and Outcomes Research

MEDPAR: Medicare Analysis and Procedure File

NCCN: National Comprehensive Cancer Network

NCI: National Cancer Institute

NED: No evidence of disease

NRCD, PSU: Northeast Regional Center for Rural Development, Penn State University

PEDSF: Patient Entitlement and Diagnosis Summary File

PSA: Prostate-specific antigen

OR: Odds ratio

QALY: Quality-adjusted life year

QIC: Quasi-likelihood under the independence model information criterion

RT: Radiation therapy

RTI: Research Triangle Institute

SD: Standard deviation

SEER: Surveillance, Epidemiology, and End Results

SRT: Salvage radiation therapy

TNM: Tumor, node, metastases

USDA: United States Department of Agriculture

WTP: Willingness-to-pay

1. INTRODUCTION

1.1. Explanation of the Issue

Approximately one-quarter to one-third of patients treated with radical prostatectomy for clinically localized prostate cancer will experience disease recurrence.[1,2] In contrast to other common cancers, disease recurrence in this setting is signaled by the detection of a serum biomarker, prostate specific antigen (PSA). Though commonly used for population-based disease screening, PSA testing was originally developed and approved for the detection of disease recurrence following treatment.[3] Following radical prostatectomy, a man's PSA level should be undetectable; if it is not, he is considered to have experienced biochemical recurrence. Patients with biochemical recurrence have no associated symptoms, and it is well established that a rising PSA level signals the early stages of treatment failure and disease recurrence.[2] If left untreated, biochemical recurrence can progress to radiographically detectable, incurable, and symptomatic metastatic disease, with a median time of eight years from detectable PSA to distant metastasis.[4]

PSA values over time, along with tumor characteristics and time from treatment to detectable PSA level, are important predictors of local versus distant recurrence and help determine the choice of secondary therapy, especially for patients initially treated with radical prostatectomy. The sooner biochemical failure is detected through rising PSA levels, the sooner secondary treatment may begin. Additionally, earlier intervention in the form of salvage radiation therapy for patients with rising PSA levels following radical prostatectomy has been associated with better outcomes.[5]

As disease recurrence is common after initial therapy, three recent clinical trials have addressed the efficacy of treating a subgroup of locally advanced prostate cancer patients with adjuvant radiation therapy (ART) immediately following radical prostatectomy. These trials sought to show whether ART would prevent future disease recurrence and result in improved outcomes.[6-8] This strategy was compared to a "wait and see" approach in which salvage radiation therapy was initiated only in response to rising PSA levels. Although only one of these trials has thus far demonstrated metastases-free or overall survival benefits,[9] all three demonstrated efficacy of immediate ART in terms of biochemically-defined recurrence-free survival.[6-8]

These trials suggest benefits associated with ART, but the associated harms are unclear. On one hand, treating all qualifying patients with ART will result in treating individuals who would have lived recurrence-free without additional treatment. As the side effects of radiation therapy can have serious quality of life implications,[10-13] the impact of radiation therapy on these patients and the associated costs should be carefully considered. On the other hand, the success of the wait and see approach is predicated upon frequent PSA testing and appropriate follow-up care in the event of a detectable PSA. Patterns of PSA surveillance after prostatectomy in real world practice are largely unknown.

Although the three trials demonstrated the superiority of immediate ART over the wait and see approach in terms of biochemically-defined recurrence-free survival, it is unclear how ART and the wait and see approach compare in clinical practice, where the population of men differs from the population of clinical trial participants.[14,15] The goal of the present research is to contribute to the understanding of post-treatment surveillance and secondary therapy in practice in the Medicare population, and to model the benefits and harms associated with ART versus the wait and see approach as they apply to the Medicare population.

With more than 200,000 new cases per year, prostate cancer is the most common noncutaneous malignancy in American men.[16] More than 32,000 men died from the disease in 2010, making prostate cancer the second leading cause of cancer death in men.[16] Between 2000 and 2007, 80% of prostate cancer cases diagnosed in Surveillance, Epidemiology, and End Results (SEER) reporting areas were localized at presentation.[17] Approximately 10% were regional and 5% were distant. Relative survival is high, with more than 95% of all men alive at five years post-diagnosis.[17] This high rate of survival along with the potential recurrence point to the importance of disease surveillance as a part of survivorship care.

According to a 2011 study of initial treatment patterns in SEER Patterns of Care data, the vast majority of clinically localized cases receive definitive local treatment in the form of surgery or radiation therapy.[18] A recent systematic review commissioned by the Agency for Healthcare Research and Quality failed to find evidence demonstrating superiority in terms of disease control for local disease of any one treatment over the others.[19] Thus, primary treatment is often determined by patient and clinician preferences[20] and varies by patient age, comorbidity, socioeconomic status, and geographic locality.[21] Men diagnosed in 2002 most often received radical prostatectomy (44.7%), followed by external beam radiation therapy (20.1%) and brachytherapy (12.3%). Other common primary treatments included watchful waiting (9%), primary androgen deprivation (hormonal) therapy (8.5%), and brachytherapy in addition to external beam radiation therapy (5.4%). Radical prostatectomy was the most common treatment for all age groups, except men ages 75 and older, for whom external beam radiation therapy was the most common, followed closely by primary androgen deprivation therapy. These percentages may not capture the full range of treatment options, as men may receive more than one type of initial or secondary therapy. For example, in this study, men who received radical prostatectomy plus adjuvant or salvage

radiation therapy were classified as receiving radical prostatectomy rather than a combination of therapies. In the case of more advanced disease, combined treatments are more often recommended than any single approach.[22]

Without a treatment superior in disease control, patients may choose treatment based on potential side effects of each treatment and their relative preference for quality of life outcomes after treatment. In a qualitative study of prostate cancer patients' concerns about treatment attributes, treatment effect on sexual, bowel, and urinary function were ranked as three of the top four concerns.[23] In direct comparisons between radical prostatectomy and radiation therapy across sexual, urinary, and bowel domains, radical prostatectomy generally tends to result in worse sexual and urinary function, while radiation therapy results in worse bowel function.[24]

When choosing whether or not to receive ART, patients must weigh the potential for improved survival against the potential side effects and associated quality of life changes due to radiation therapy. Many studies evaluate the effect of a single treatment on quality of life,[25-30] but few evaluate the effect of adjuvant or salvage therapies. Two recent longitudinal analyses of men in the Cancer of the Prostate Strategic Urologic Research Endeavor registry evaluated the effect of salvage radiation therapy on quality of life.[31,32] In one study, men who received salvage radiation therapy had worse physical function before and after radiation therapy compared to men who received only radical prostatectomy.[31] This finding is not surprising as the men who received salvage radiation therapy received salvage therapy due to disease recurrence, whereas the radical prostatectomy-only group could be considered recurrence-free.

For patients diagnosed with prostate cancer in 2002, Medicare paid on average $18,261 for initial care.[33] In comparison, initial costs for patients diagnosed in 1991 totaled $200 more (in adjusted dollars). Medicare costs for initial treatment of breast, colorectal, and lung cancer in 2002 were $20,929, $41,134, and $39,891, respectively.

Although Medicare paid the least, on average, for initial treatment of prostate cancer, the high incidence of prostate cancer creates a high total cost burden. Additionally, many costs associated with prostate cancer treatment may be incurred several years after diagnosis. As an initial therapy, active surveillance leads to low initial costs but does not preclude surgery or radiation therapies in the future, which have much higher costs.

1.2. Specific Aims

The choice of initial treatment (and secondary therapy should initial treatment fail) involves balancing treatment side effects, the potential for disease control, current and future costs, and the intensity of surveillance care. The present research explores these trade-offs through three study aims:

Aim 1: **To examine patterns of PSA surveillance testing among elderly men treated with radical prostatectomy for non-metastatic prostate cancer.** Rising PSA levels following surgery are the primary indication of disease recurrence, but little is known about how often PSA is measured in men after initial treatment. This aim uses SEER data linked with Medicare claims to fill this knowledge gap and to identify groups who may not be receiving high-quality survivorship care in terms of adherence to guideline-recommended PSA surveillance.

Aim 2: **To evaluate the validity of the SEER radiation therapy treatment variable.** SEER provides information on whether radiation therapy was received, recommended, or not received, as well as information on the timing of radiation therapy administered adjuvant to surgery. Overall agreement is high in SEER-Medicare about receipt of radiation therapy,[34] but no research has demonstrated whether this holds true for ART after prostatectomy. ART may be administered months after surgery and may be recommended only after examination of tumor pathology. These timing issues may lead to incomplete capture of ART in SEER, which could have implications for the use of SEER in examining treatment patterns.

Aim 3: **To compare through a decision model the wait and see approach versus ART following radical prostatectomy.** Part of the concern with treating all qualifying men with ART is the unnecessary treatment of men whose disease will never progress following surgery. To date, this additional treatment's negative side effects have been described but neither quantified nor compared to potential survival benefits. I constructed a cost-utility model which allowed for the evaluation of the two treatment pathways in patient populations facing different risks of disease recurrence and allowed me to evaluate assumptions about disease progression and treatment-related side effects.

1.3. Organization of this Dissertation

To place my research into the context of current approaches to prostate cancer treatment, I conducted an extensive literature review that is presented in Chapter 2. This chapter provides more information on the staging and course of disease in prostate cancer, radiation therapy as implemented in practice and in clinical trials, and describes extant comparative and cost-effectiveness analyses in prostate cancer care. Chapter 3 contains details about the data sources, sample construction, and methods used to fulfill the three specific aims. Chapters 4 through 6 are self-contained manuscripts addressing the specific aims. Each of these chapters contains an abstract, introduction, and conclusion relevant to the specific aim under examination. The last chapter discusses the research findings, examines the limitations and study strengths of the data, approaches and conclusions, and lays out a research agenda based upon the results from the research.

2. BACKGROUND

2.1. Prostate Cancer Diagnosis, Staging, and Treatment Guidelines

The prostate is a small, walnut-sized gland located below the bladder and in front of the rectum. Luminal epithelial cells in the prostate produce prostate-specific antigen (PSA), and elevated PSA levels in the blood are most often the first sign of prostate cancer.[35] (The value of PSA testing for cancer screening has received much attention in research and popular media,[36] but an examination of the utility of PSA screening is beyond the scope of the current research.) Diagnosis is confirmed using a transrectal ultrasound-guided biopsy.[37] The strongest risk factors for disease are age, race, and family history,[38-41] while associations between hormone level, diet, obesity, and physical exercise and disease are suspected but less well-established.[41]

Prostate cancer is staged according to the tumor, node, metastases (TNM) system, which incorporates primary tumor size and extension, lymph node involvement, and distant metastasis.[37] In most patients, digital rectal exam is the primary method of assessing clinical stage. Complete pathological staging requires radical prostatectomy, regional node examination, and histological analysis. The clinical and pathologic American Joint Committee on Cancer (AJCC) primary tumor definitions (T and pT), described in Table 1, combined with description of lymph node involvement (N0 for no regional nodes, N1 for metastasis in regional nodes, and NX for not assessed), and an indicator for metastatic disease (M0 for no distant metastasis and M1 for distant metastasis) combine to form the TNM stage.

Table 1. American Joint Committee on Cancer Prostate Cancer Staging Definitions[42]

Primary Tumor, Clinical	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor neither palpable nor visible by imaging
T1a	Tumor incidental histologic finding in 5% or less of tissue resected
T1b	Tumor incidental histologic finding in more than 5% of tissue resected
T1c	Tumor identified by needle biopsy (for example, because of elevated PSA)
T2	Tumor confined within prostate*
T2a	Tumor involves one-half of one lobe or less
T2b	Tumor involves more than one-half of one lobe but not both lobes
T2c	Tumor involves both lobes
T3	Tumor extends through the prostate capsule**
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles, such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall
Primary Tumor, Pathological***	
pT2	Organ confined
pT2a	Unilateral, one-half of one side or less
pT2b	Unilateral, involving more than one-half of side but not both sides
pT2c	Bilateral disease
pT3	Extraprostatic extension
pT3a	Extraprostatic extension or microscopic invasion of bladder neck****
pT3b	Seminal vesicle invasion
pT4	Invasion of rectum, levator muscles, and/or pelvic wall

*Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c.
**Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified not as T3 but as T2.
***There is no pathologic T1 classification
****Positive surgical margin should be indicated by an R1 descriptor (residual microscopic disease).

The Gleason score is the primary method of grading prostate cancer.[37] The total Gleason score is the sum of two individual patterns (on a scale of one to five) associated with histopathological architecture.[43] A Gleason score of seven or greater is generally thought to be indicative of higher grade disease.[35] Gleason score, TNM stage, and PSA

value are all strongly related to prognosis and frame clinical risk stratification, which in turn frames treatment recommendations.[22] The D'Amico risk groups, as described in Table 2, are commonly used to categorize patients with clinically localized disease by risk of disease recurrence following initial treatment.[44]

Table 2. Definitions of D'Amico Risk Categories[44]

Risk	Stage		PSA		Gleason Total
Low	T1c, T2a	AND	≤ 10 ng/mL	AND	≤ 6
Intermediate	T2b	OR	>10 ng/mL, ≤20 ng/mL	OR	7
High	T2c	OR	>20 ng/mL	OR	>7

Note: PSA: Prostate-specific antigen; T-stage based on American Joint Committee on Cancer staging guidelines; ng/mL: nanograms per milliliter

The National Comprehensive Cancer Network (NCCN) recommends treatment options based on a similar risk stratification scheme as that defined by D'Amico (Table 3),[22] with the addition of "Very Low" and "Very High" risk categories at either extreme. The treatment guidelines published by NCCN are based on clinical evidence, where available, and expert consensus where evidence is inconclusive. Active surveillance is a valid treatment option for all patients with very low or low risk disease, regardless of life expectancy. Patients with low risk disease and a life expectancy of more than 10 years are also recommended to consider external beam radiation therapy, brachytherapy, or radical prostatectomy (with the potential for future adjuvant or salvage treatment if the tumor specimen possesses adverse pathological features). Patients with intermediate risk disease may be treated with active surveillance (if life expectancy is less than 10 years), external beam radiation therapy, brachytherapy, radical prostatectomy, or a combination of treatments with or without androgen deprivation therapy (ADT). Men with high or very high risk disease may be treated with external beam radiation therapy and ADT or radical prostatectomy (with ADT given for node positive disease). Androgen

deprivation therapy (hormone) is not recommended alone as an initial treatment modality except for in men with locally advanced or metastatic disease.[22]

Table 3. National Comprehensive Cancer Network Recurrence Risk Groups for Clinically Localized and Locally Advanced Disease.

Risk	Stage		PSA		Gleason Total
Very Low*	T1c	AND	< 10 ng/mL	AND	≤6
Low	T1-T2a	AND	< 10 ng/mL	AND	2-6
Intermediate**	T2b-T2cb	OR	10-20 ng/mL	OR	7
High**	T3a	OR	>20 ng/mL	OR	8-10
Very High	T3b-T4				

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*Additional necessary factors for very low risk include fewer than three biopsy cores positive, ≤50% cancer in each core, and PSA density < 0.15 ng/mL/g, **Patients with multiple adverse factors may be shifted into the next highest group.

Note: PSA: Prostate-specific antigen; T-stage based on American Joint Committee on Cancer staging guidelines, ng/mL: nanograms per milliliter; ng/mL/g: nanograms per milliliter per gram.

In recent years, the overdiagnosis and overtreatment of low risk men have received much attention in research and popular media.[45,46] Although these are major issues in prostate cancer care, there are still a significant number of men with intermediate and high risk disease for whom undertreatment may be the more pressing concern. Many of these men may face a risk of disease recurrence despite definitive local treatment with curative intent. The use of recurrence risk as a tool to choose initial treatment highlights the fact that for many men, initial treatment alone will not provide a cure.[1,2] The end of initial treatment signals the transition from cancer patient to cancer survivor, and, according to the Institute of Medicine, individuals live as cancer survivors until disease recurrence, a second cancer, or death.[47] Following receipt of definitive local therapy, prostate cancer survivors transition into a period of disease surveillance based primarily on serum PSA monitoring. Disease surveillance through the use of repeated PSA tests is a critical part of survivorship care, as increasing PSA levels, particularly

following radical prostatectomy, are often the first sign that initial treatment has failed to achieve complete disease control.[2]

2.2. Prostate Cancer Surveillance Compared to Other Cancers

In contrast to other common malignancies, the patterns of care and health services utilization of prostate cancer survivors have received less study, particularly in terms of surveillance. Surveillance, in contrast to screening, refers to tests and medical monitoring aimed at detecting disease recurrence rather than detecting new disease. Breast, colorectal, and prostate cancer treatment guidelines all contain guidance for post-treatment disease surveillance, specifically regarding the use of mammography,[48] colonoscopy,[49,50] and PSA testing,[22] respectively. The use of surveillance colonoscopy after colorectal cancer diagnosis and treatment has been well-documented in multiple populations,[51-54] as has the use of mammography after breast cancer diagnosis and treatment.[55-57] In contrast, there is a relative paucity of literature regarding the utilization of PSA testing among prostate cancer survivors following definitive primary treatment.

A study of colorectal cancer patients enrolled in National Surgical Adjuvant Breast and Bowel Project clinical trials found high use of colonoscopy among survivors.[52] Surveillance colonoscopies are recommended at 12 months after surgery[58] and at least once every five years, and among patients with five to seven years of survivorship, 96.5% had received a colonoscopy within the previous five years.[52] This high rate of surveillance remained stable among patients with more than five to seven years of survivorship.

As clinical trial enrollees may not be representative of the general colorectal cancer population, other studies have sought to document surveillance patterns in health maintenance organization (HMO)[51,54] and population-based samples.[53] In a study of the Cancer Care Outcomes Research and Surveillance study population, less than half of eligible colorectal cancer survivors received colonoscopy within 14 months after

treatment.[53] Although the difference in surveillance between non-Hispanic whites and non-Hispanic blacks was not statistically significant, notable regional variations were observed.[53]

Surveillance mammography has been shown to reduce mortality in elderly breast cancer patients diagnosed with and treated for early stage disease;[59] however, not all women receive appropriate post-treatment surveillance. A recent study found that, regardless of race or dual Medicare/Medicaid eligibility, women who received breast conserving surgery with radiation therapy were more likely to receive surveillance mammography than women treated with breast conserving surgery alone.[56] Another study reported that patients who are older, African-American, and unmarried were less likely than other women to receive surveillance mammography.[60]

It is unknown whether the surveillance patterns related to region in colorectal cancer and race in breast cancer observed in colorectal and breast cancer apply to prostate cancer. Without knowledge of who is at risk for receiving inadequate follow-up care, it is impossible to design programs and policies to improve care in at-risk populations. Follow-up care, as an important component in cancer survivorship, presents another phase in cancer care where racial and socioeconomic disparities observed in treatment may persist. As part of this research I have identified these at-risk populations and documented the extent to which observed follow-up surveillance diverges from recommended surveillance. This analysis is presented in full in Chapter 4.

2.3. Prostate-specific Antigen Testing in Prostate Cancer Surveillance Care

Detectable or rising PSA levels after prostate cancer treatment are often the first indicator of recurrent disease, and an early diagnosis of treatment failure can facilitate initiation of salvage therapy.[61] The effectiveness of post-prostatectomy salvage radiation therapy in achieving disease control as measured by PSA response has been demonstrated, [5] and the timing of salvage therapy initiation also may contribute to

improved outcomes. Multiple series have suggested that treatment response and long-term survival rates are sensitive to bulk of disease, measured by PSA level, at time of salvage treatment.[62-64] Whereas PSA monitoring following every type of initial treatment is recommended, PSA values following radical prostatectomy are more easily interpretable than PSA values following other types of treatment.[65] It is for this reason that I have focused the present research on disease surveillance in patients receiving radical prostatectomy as a definitive local therapy.

Given the putative benefits of early detection of recurrence in many patients, appropriate post-treatment surveillance is essential for men who receive prostatectomy to treat prostate cancer. The 1997 NCCN Guidelines called for PSA testing every 6 months over five years and annually thereafter for men who received potentially curative initial therapy.[66] The testing period for the first five years changed from every 6 months to every 6-12 months in the second version of the 2007 Guidelines.[67] This remains the recommended testing period.[22] Evidence is lacking, however, as to whether men actually receive recommended PSA surveillance after treatment of clinically localized prostate cancer.

There is a paucity of data on follow-up surveillance in prostate cancer survivors despite demonstrated racial and geographic differences in prostate cancer treatment and mortality.[68,69] In a small, community-based cohort study of patients diagnosed with prostate cancer between 1991 and 1992 receiving treatment in New Haven and Hartford, Connecticut, the proportion of men who did not receive a PSA test following prostate cancer diagnosis ranged from 22% to 29% in any given year after diagnosis.[70] Among those men who were followed for five full years, 7% never received a PSA test. Fewer than half of men (45%) received at least one test each year during the entire follow-up period, which ranged from one to nine years. African-American race, time since diagnosis, and older age were associated with fewer tests per year. Testing

frequency also varied with type of initial treatment. Annual testing was more common among those men who received radical prostatectomy, compared to those men who received radiation therapy or watchful waiting. The authors do not report rates of salvage radiation therapy. Additionally, this study did not account for patient socioeconomic characteristics such as insurance status, income, or education, and all of these factors are likely to be correlated with both race and follow-up care.[71] Although this study is the only examination of post-diagnosis surveillance patterns in the literature, it is limited by the small sample and single location. Furthermore, the patient surveillance occurred in the mid-1990s, before formal recommendations for PSA surveillance practices were promulgated by practice guidelines panels.

A slightly more recent survey of members of the American Urological Association (AUA) provides more information about the surveillance practices of U.S. and international urologists.[72] This 1997 survey targeted urologists who performed prostatectomy procedures and provided patient follow-up. As there were no established guidelines in place for surveillance at the time of the study, the survey results serve to illustrate urologists' recommendations rather than their actual adherence to a standard survivorship care plan. Nevertheless, the study findings provide the best available information about how urologists would ideally follow patients post-prostatectomy. Office visits, digital rectal exams (DREs), PSA testing, and urinalysis were the most commonly recommended follow-up practices and were typically recommended three or four times a year for the first year following surgery.[72] The recommended frequency of tests decreased with increasing time from surgery. The majority of respondents recommended the same surveillance schedule for patients with stage T1-T2N0M0 disease as patients with stage T3a-T3cN0M0 disease.

Despite recommending a rigorous follow-up schedule, only half of respondents felt that routine follow-up testing could detect a disease recurrence early enough to

provide curative treatment. In fact, the main motivating factors behind recommending follow-up testing were concerns about patient expectation, legal liability, and patient referrals. However, the results from this study does not reflect current surveillance motivations, as the survey took place nearly 15 years ago. Additionally, sample inclusion criteria are an obvious limitation, given that many patients may receive follow-up care from providers other than the urologist who performed their prostatectomy.[73,74] Findings are also limited by self-report and the relatively small number of cases managed by each respondent on average.

2.4. PSA Recurrence and Elevation after Initial Treatment and Disease Progression

The seminal, and most commonly cited, description of prostate cancer progression following PSA elevation after radical prostatectomy comes from a cohort of 1,997 men treated at the Johns Hopkins Hospital between 1982 and 1997 and followed for a median of 5.3 years.[4] All men received PSA tests and DREs every three months for the first year following surgery, every six months for the second year, and annually in the third year and beyond. In this cohort, actuarial metastases-free survival at 15 years was 82%. Median time from PSA elevation to metastatic disease was 8 years, and median time from metastatic disease to death was five years. The analysis did not include men who received salvage radiation therapy upon PSA elevation and responded to therapy (as evidenced by PSA response), as they were considered to have local recurrence only. Thus, the disease progression patterns in this cohort represent the course of prostate cancer in absence of curative secondary therapy.

Based on the disease progression documented in the Hopkins cohort, when biochemical recurrence occurred, it most often (in approximately 75% of cases) occurred in the first five years following surgery.[4] Among the men who experienced biochemical recurrence, 44.7% had elevated PSA levels in the first two years following surgery.[4]

These results highlight the importance of disease monitoring through PSA surveillance, particularly in the period immediately following treatment.

2.5. Clinical Trials: Adjuvant Radiation Therapy and the Wait and See Approach

For patients presenting with pathological stage T3 (pT3) disease, 10% to 50% of these men may not achieve disease control with prostatectomy alone.[75] In 2005, the first of three major clinical trials evaluating the use of adjuvant radiation therapy (ART) after prostatectomy provided evidence of the benefit of ART for certain high-risk prostate cancer patients.[7] The other two trials published similar results in 2006 and 2009.[6,8] This time period also saw the publication of a large retrospective study reporting durable disease response to salvage radiation therapy following prostatectomy (discussed in Section 2.6).[76] The 2010 NCCN Guidelines were revised accordingly to reflect the trial and retrospective study findings. Part of the "Principles of Radiation Therapy" in the 2010 guidelines reads, "evidence supports offering adjuvant/salvage RT in all men with adverse pathologic features or detectable PSA and no evidence of disseminated disease." (Section PROS-C)[22] In this context, RT refers to external beam radiotherapy, and adverse pathologic features are positive margins, seminal vesicle invasion, extracapsular extension or detectable PSA.[22] This recommendation was made with lower-level evidence and reflected NCCN consensus. In contrast, a recommendation in the 1999 NCCN Guidelines to consider "radiotherapy if status post-radical prostatectomy with positive margins of high-grade disease or gross residual disease" was classified as "somewhat controversial."[77]

Among the three clinical trials, patients have been followed the longest in the SWOG (formerly the Southwest Oncology Group) 8794 trial, which recruited patients in the United States between 1988 and 1997.[8] This trial was designed to test the hypothesis that ART after prostatectomy results in improved progression-free survival compared to patients who receive either salvage radiation therapy upon biochemical

recurrence or no radiation therapy (the control group). Among patients randomized to receive ART, PSA relapse occurred in 34.9% of patients. PSA relapse occurred in 64% of the control group. Median time to PSA relapse in the adjuvant group was 10.3 years, which was significantly longer than the median PSA relapse-free survival in the control group (3.1 years). ART also increased disease relapse-free survival (defined by observable and measurable disease, excluding PSA relapse) and reduced the risk of initiation of hormonal therapy. Despite a median follow-up of more than 10 years, results showed no significant differences in metastases-free or overall survival.[8]

A follow-up publication to the initial SWOG trial results (presented above) reported on metastases-free and overall survival.[9] With a median follow-up of more than 12 years, survival curves for the radiation therapy group and the control group differed significantly ($p = 0.023$). The 10-year estimate of metastases-free survival was 71% in the ART group and 61% in the control group (significant with $p = 0.016$).

The European Organisation for Research and Treatment of Cancer (EORTC) 22911 clinical trial began recruitment in 1992 to test the same hypothesis that ART after prostatectomy results in improved progression-free survival compared to patients who receive either salvage radiation therapy upon biochemical recurrence or no radiation therapy.[7] The inclusion criteria for this study were the same as those for the SWOG study. Five-year biochemical progression-free survival was 74.0% in the ART group compared to 52.6% in the control group. With a median follow-up of only five years, the trial has not yet produced results on metastases-free or overall survival. More follow-up time will be needed to assess whether the survival benefits observed in the SWOG trial apply to the EORTC trial as well.

Additional subgroup analysis of the tumor pathology of 552 patients in the EORTC trial revealed differential benefits associated with ART in patients with positive surgical margins.[78] After controlling for patient characteristics, results indicated no

difference in biochemical recurrence-free survival between patients with negative margins in either the adjuvant or control groups ($p > 0.1$) and the patients with positive margins in the adjuvant group ($p = 0.07$). Only the patients with positive margins in the control group fared significantly worse at five years post-treatment. For every 1,000 patients with positive margins, ART would prevent 291 cases of biochemical recurrence at five years. In contrast, ART would prevent only 88 biochemical recurrences for every 1,000 patients with negative margins. Postoperative PSA, Gleason score, and seminal vesicle invasion were not found to be predictive of biochemical recurrence-free survival.

Another European trial of the same hypothesis with comparable pathological stage inclusion criteria produced very similar results. Whereas the EORTC and SWOG trials did not require an undetectable PSA following prostatectomy, the ARO 96-02/AUO AP 09/95 trial (conducted by the German Cancer Society; hereafter referred to as ARO) added this feature as an additional inclusion criterion. Patients who achieved an undetectable PSA after radical prostatectomy were randomized to immediate radiation therapy or a wait and see approach to salvage radiation therapy. The results were remarkably similar to those seen in the other two trials, despite slightly different inclusion criteria and trial protocol. Biochemical recurrence-free survival at five years was 72% in patients randomized to ART, which was significantly greater than the 54% observed in the control group.[6] Univariate (but not multivariate) subgroup analyses also indicate a progression-free survival benefit associated with ART for patients with positive surgical margins.[6]

Together, these three trials and a contemporary retrospective series (discussed in the following section)[76] support secondary (both adjuvant and salvage) radiation therapy after prostatectomy, but it is unclear whether ART is superior to salvage radiation therapy delivered at the first sign of biochemical recurrence. Many of the trial participants in the SWOG and EORTC trials never achieved an undetectable PSA level

following radical prostatectomy. In current-day practice, radiation therapy given to these patients would be considered salvage rather than adjuvant, as adjuvant radiation therapy is radiation therapy given to patients with no evidence of disease but a high risk of disease recurrence.

Not all trial participants who experienced disease recurrence received salvage radiation therapy at the time of recurrence, and the trials were not consistent in their definition of biochemical recurrence. Three ongoing prospective trials are examining the comparison of ART to salvage therapy delivered at the first sign of biochemical recurrence,[79-81] but until these results are published, the timing and delivery of secondary radiation therapy remains largely based on shared decision-making between patients and physicians.[81]

2.6. Retrospective Studies of Adjuvant and Salvage Radiation Therapy

In the absence of clinical trials demonstrating the superiority of ART over timely initiation of salvage radiation therapy, several retrospective studies have sought to quantify potential benefits associated with salvage radiation therapy and prognostic factors related to the success of salvage radiation therapy.[76,82] One such study evaluated the outcomes from 501 patients with disease recurrence after radical prostatectomy between 1987 and 2002.[76] In a multivariate analysis, negative surgical margins, a Gleason score of 8 to 10, pre-radiation therapy PSA greater than 2.0 ng/mL, seminal vesicle invasion, and a PSA doubling time of 10 months or less were associated with failure of salvage radiation therapy to prevent disease progression. That is, disease progression in these patients is more likely to be characterized as distant recurrence rather than local recurrence and therefore may not be curable with secondary local therapy.

To better understand the probability of complete response to salvage radiation therapy following PSA recurrence after radical prostatectomy, the authors expanded

their retrospective cohort to 1,540 patients undergoing salvage radiation therapy between 1987 and 2005.[5] In this cohort, the PSA level before the initiation of salvage radiation therapy was a significant predictor of the likelihood of success of salvage therapy, with lower PSA values associated with better outcomes. This finding emphasizes the importance of close PSA monitoring following radical prostatectomy, as there may be a window of opportunity following PSA recurrence where salvage treatment is most effective.

Although the three recent clinical trials demonstrated improved biochemical recurrence-free survival associated with ART, particularly in select patient subgroups, it is not clear that ART is superior to a salvage approach in which salvage radiation therapy is administered at the first sign of an increasing PSA following surgery.[5,76,83] The latter approach can result in fewer patients receiving additional therapy compared to the former approach, but its successful implementation is predicated upon appropriate follow-up care after surgery. ART for patients meeting eligibility criteria for the trials may result in additional treatment-related morbidity, but can decrease the risk of disease progression in patients who may otherwise not receive appropriate surveillance and follow-up.

2.7. ART in Practice

Although the three clinical trials clearly demonstrate the efficacy of ART over a wait and see approach, particularly in some subgroups, the effectiveness of ART in practice is not known. Clinical trial populations may differ in significant ways from the Medicare population,[14] and population differences may reduce result generalizability. In the specific case of the ART trials, the average age of trial participants ranged from 64 to 65, and all three trials limited recruitment to participants younger than age 76.[6-8] In contrast, only 53% of Medicare enrollees were between the ages of 65 and 74 in 2009,[84] and the average age of the Medicare population at prostate cancer diagnosis is 67.[85] To

the best of my knowledge, there has yet to be an analysis of the course of disease specifically in Medicare patients with pT3N0M0 tumors or pT2 tumors with positive surgical margins.

Two recent studies evaluated the use of ART in the SEER population and established patterns of care in the period before and after the presentation and publication of clinical trial data.[86,87] One study examined the use of ART in men diagnosed with prostate cancer between 2004 and 2005 with pT3 disease who had undergone radical prostatectomy and had extracapsular extension and positive surgical margins.[87] In this small (by SEER standards) sample of 1,427 men, 18.2% received ART. Under the 2010 NCCN Guidelines, ART should be considered for these men (although salvage radiation therapy would still be an acceptable secondary therapy). Receipt of ART varied widely by SEER region, but there was no consideration of patient characteristics, and sample sizes for some regions were very small (ranging from 12 to 352 men).

A more thorough analysis of ART use in the SEER population focused on the recommendation for post-prostatectomy radiation therapy between 2000 and 2007.[86] Men in this sample underwent prostatectomy for N0M0 prostate cancer. Eligible men had tumors classified as pT3 or pT2 with positive surgical margins. Of the 21,917 men meeting inclusion criteria, 13.5% received a recommendation for ART. The authors document a surprising significant, negative relationship between year of diagnosis and recommendation for ART. That is, rates of ART recommendation decreased over time. There was no difference in recommendations in the periods before and after the presentation of results from EORTC 22911 and SWOG 8794. These results reflect treatment decisions made before the publication of the overall survival benefits associated with ART, so the lack of a trend may reflect clinician reluctance to recommend additional treatment without a proven survival benefit. However, rates of

ART for other cancers have responded to presentations of clinical trial results.[88,89] Regardless, it will be many years before the effect of the ART trial results on clinical practice patterns can be fully established.

2.8. Measuring Adjuvant and Salvage Radiation Therapy in SEER

The SEER program (discussed in more detail in Chapter 3) provides information on first course of treatment following a cancer diagnosis for people living within registry areas.[90] Historically, initial treatment was captured if it occurred within four months of diagnosis,[90] but the newer editions of the SEER coding manual instruct that all treatments included in a documented treatment plan be considered as part of the initial course of therapy, regardless of when they occur.[91] The most recent comparison of SEER and Medicare reports of radiation therapy treatment was published in 2002 and used data from patients diagnosed with prostate cancer from 1991 to 1996.[34] Since this time, there has been growing recognition that ART may offer benefits for select prostate cancer patients, which combined with variations in the timing of ART warrants a contemporary comparison of SEER and Medicare treatment variables.

Although the changes in the SEER coding manual are now designed to capture more initial therapy delivered over time, the four months from diagnosis window could easily fail to include ART delivered in earlier time periods. ART as defined in the clinical trials was initiated within approximately four months of surgery.[8] In a study of men receiving care at Veterans Affairs Medical Centers, the mean time from diagnosis to surgery was 76 days for African-American men and 68 days for Caucasian men.[92] Although care received by men at Veterans Affairs Medical Centers may not be representative of care received by the Medicare population in general, it is quite likely that men may experience a two-month delay between diagnosis and surgery, as current surgical practice dictates a minimum of six weeks between biopsy and surgery.[93] ART delivered four months after surgery would be delivered six months after diagnosis,

pushing it beyond the four month window historically captured by SEER. Additionally, the decision to provide adjuvant radiation therapy may not be made until after pathologic examination of surgical margins, so it is conceivable that radiation therapy delivered in the adjuvant setting might not be part of the initial documented treatment plan.

A number of studies in the breast cancer literature have sought to investigate the degree of agreement between the treatment reported in SEER and the actual treatment received.[94-96] Two of these studies compared SEER records to Medicare claims,[94,95] whereas the third compared SEER records to self-reported treatment received.[96] For women diagnosed from June 2005 to February 2007 in Los Angeles and Detroit, SEER records failed to capture radiation therapy for 21% of women who say they received it.[96] Rates of underascertainment varied by region, chemotherapy and mastectomy receipt, stage, income, and diagnosis at a hospital not accredited by the American College of Surgeons. Additionally, in Los Angeles, underascertainment was associated with younger age. The authors conclude that the use of SEER (or other registries) alone may result in underascertainment of radiation therapy, particularly when there is a delay or increased time between surgery and radiation therapy.[96] These studies support further investigation of SEER treatment data quality in the setting of evolving standards of care for prostate cancer. The analysis presented in Chapter 5 addresses this issue by evaluating the suitability of SEER treatment data as a surrogate for full Medicare claims data.

2.9. Comparative Effectiveness Research and Cost-utility Analysis

Without strong clinical evidence demonstrating the superiority of a single prostate cancer treatment method over the others, treatments are often compared through the use of observational comparative effectiveness research. According to the Institute of Medicine, comparative effectiveness research compares the benefits and harms of alternative methods of disease prevention, treatment, diagnosis, or care delivery. The

purpose of comparative effectiveness research is to aid in informed decision making on the part of consumers, physicians, and policy makers.[97]

Comparative effectiveness research has gained popularity in recent years due to funding provided by the American Recovery and Reinvestment Act of 2009.[98] In contrast to comparative effectiveness research, cost-effectiveness research incorporates costs into the equation when evaluating treatment alternatives. Cost-effectiveness models compare the costs and outcomes associated with two or more competing options to aid decision makers in selecting the strategy that will result in the greatest net benefit.[99] Cost-effectiveness analysis can be used to compare a new intervention (which could be a treatment, a screening strategy, a surgical technique, etc.) to existing standard practice. Decision analysis, a particular type of cost-effectiveness analysis, incorporates variability and uncertainty about inputs.[100] This type of analysis allows for sensitivity analyses in which assumptions about costs, probabilities, and outcomes can be modified to determine the stability of results.[100]

Cost-utility analysis, a type of cost-effectiveness analysis, converts all benefits and risks of treatments into a standard measure called quality-adjusted life years (QALYs). This measure allows for the comparison of the relative effectiveness of interventions across diseases or techniques.[101] The standard outcome in cost-utility studies is an incremental cost-effectiveness ratio (ICER), which is reported in dollars per QALY. As a well-designed cost-utility analysis incorporates all harms and benefits of given interventions, the ICER can be seen as the total cost per additional QALY gained provided by one intervention over another.[102]

ICERs can range from cost-saving (or "dominating"), in which intervention A results in lower costs *and* better outcomes than intervention B, to "dominated," whereby intervention A results in both higher costs and worse outcomes than intervention B. More commonly, cost-utility analysis results demonstrate that a new intervention both

improves outcomes and induces higher costs. Generally, in the U.S., an intervention or program is considered cost-effective if the ICER is less than $50,000 per QALY.[103] However, as this threshold is not based in theory or evidence and has not been adjusted for inflation in the cost of medical care,[104] it is helpful to both consider the sensitivity of the ICER to model assumptions and to place the ICER in the context of the cost-effectiveness of other health interventions. A recent survey of American Society of Clinical Oncology members found that U.S. medical oncologists were willing to prescribe treatments that cost more per QALY for life-prolonging therapies than for treatments that improved quality of life but did not improve survival.[105] On average, survey respondents were willing to prescribe life-prolonging treatments with an ICER of $245,972 per QALY and quality of life-improving treatments with an ICER of $119,082. These results highlight the variation in the value of a QALY, even within the same sample. Additionally, the variation in the value of a QALY demonstrated in the relatively homogenous sample of U.S. medical oncologists highlights the difficulty in establishing a cost-effectiveness threshold that would be acceptable across a wide range of disciplines and interventions.

2.10. Cost-utility Analysis in Cancer

A review of cost-utility analyses in cancer found 242 original cancer-related studies published through 2007.[101] These articles all were included in the Tufts Medical Center Cost-Effectiveness Analysis Registry, which currently maintains information on more than 2,400 peer-reviewed cost-effectiveness analyses.[106] A relatively small proportion of all cost-utility analyses conducted during this time frame pertained to cancer (14%).[101] Of the cancer cost-utility analyses included in the review, 73% evaluated interventions related to treatment and 19% evaluated secondary prevention measures such as cancer screening. Pharmaceuticals were most often analyzed (53% of studies), followed by medical procedures (18%) and screening strategies (16%).

Overall adherence to methodological standards in these studies is good and has been improving over time.[101]

As the Tufts registry limits inclusion to those articles that present ICERs in terms of dollars per QALY, it may not provide a complete picture of cost-effectiveness and cost-utility analysis use in prostate cancer. Some recent prostate cancer decision analyses present outcomes in terms of dollars per life year saved.[107,108] More common are analyses of utility or cost alone. Recent comparative effectiveness and cost-utility research studies in prostate cancer have focused on chemoprevention,[107,109,110] PSA screening,[108] treatment for early stage disease,[111-114] treatment for biochemical recurrence,[115] risk-prediction tools,[116] and type of radiation therapy.[117]

2.11. Modeling ART versus the Wait and See Approach to Salvage Radiation Therapy

A recent study performed a decision analysis comparing the quality of life benefits of ART and a wait and see approach to radiation therapy after radical prostatectomy.[118] The authors found that the wait and see approach resulted in 6.8 QALYs over ten years compared to 6.13 QALYs over ten years for ART. However, ART was found to be more effective than the wait and see approach in terms of 10-year PSA recurrence-free survival, metastasis-free survival, and overall survival.

The model and analysis presented in Chapter 6 extends and improves upon this published study in several ways. First, the inclusion of cost in the decision analysis provides a way to compare ART to other interventions in cancer and prostate cancer. Second, I have evaluated the sensitivity of my results to all parameter assumptions through a full probabilistic sensitivity analysis rather than the three-way sensitivity analysis used in the previous model. Additionally, I followed patients for their lifetime rather than over a ten-year time period and incorporated discounting, which the previous model did not.

3. DATA AND ANALYTICAL METHODS

This chapter introduces the data sources and methods for all three research aims. Aims 1 and 2 are retrospective studies using data from the linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database, which is described below along with each aim's sample inclusion criteria. Aim 3 was analyzed using a cost-utility model, which was populated with data from published literature. Model inputs included disease progression probabilities, utilities for prostate cancer disease states and treatment-related side effects, and costs related to adjuvant and salvage radiation therapy and treatment of metastatic disease.

3.1. Data Sources

3.1.1. SEER-Medicare Data (Aims 1 and 2)

Data for the analyses of Aims 1 and 2 came from the linked SEER-Medicare claims database. The SEER program collects population-based data on all incident cancer cases among residents of areas with participating registries. These cancer cases can be linked to Medicare claims for Medicare participants who participate in fee-for-service (FFS) insurance plans. Currently, 28% of the U.S. population lives in area captured by the SEER program, and the most recent SEER update contains information from registries covering 17 reporting areas on 27 cancer sites and sub-sites through 2007. The SEER registries collect information on patient demographics, cancer site, extent of disease, tumor characteristics, initial treatment, and vital status follow-up.[119] Patient demographics include age at diagnosis, marital status, race/ethnicity, and county of residence at diagnosis. The SEER program conducts annual studies in SEER areas to evaluate the quality and completeness of the data reported to the registry.[90]

Medicare is the primary health insurance provider for 97% of the U.S. population aged 65 and older. All beneficiaries receive Part A benefits, which cover inpatient hospital care, skilled nursing facilities, home health, and hospice care. Ninety-five percent of beneficiaries pay a monthly premium for Medicare Part B, which covers physician services, outpatient care, and durable medical equipment and can take the form of a FFS or health maintenance organization (HMO) plan. The Medicare Enrollment Database, which can be linked to SEER data, contains information on enrollment, entitlement, HMO membership, and demographics for each individual in the Medicare program.[90]

The first SEER registry data linkage to the Medicare Enrollment Database occurred in 1991.[90] The current data linkage contains data on all cancer diagnoses through December 31, 2007, and all Medicare claims through December 31, 2009 for individuals participating in Medicare FFS plans.[119] The Medicare files available through the linkage include claims from hospital, outpatient, physician, home health, and hospice providers. Each file contains patient demographics, date of service, diagnostic and procedure codes, and associated charges and reimbursement.[90]

Detailed claims are not available for the 15% of Medicare participants enrolled in HMO plans. HMO penetration rates vary substantially across SEER reporting areas, with California having the highest HMO penetration at 38%.[90] The proportion of Medicare beneficiaries in SEER areas enrolled in HMOs is greater than the nationwide proportion of beneficiaries enrolled in HMOs, but this difference has decreased over time.[90] Nationwide, the proportion of Medicare beneficiaries participating in HMO plans averaged 13% from 2001 to 2005, and 18% of Medicare beneficiaries in SEER areas participated in HMO plans over the same time period.[120]

The SEER-Medicare dataset is composed of several different files. The Patient Entitlement and Diagnosis Summary File (PEDSF) contains all of the tumor and

treatment data reported by SEER registry, Medicare entitlement and enrollment information, and U.S. Census-linked socioeconomic information at the tract and ZIP code level. Each row of the dataset contains all information on all cancers for a single individual. The Medicare analysis and procedure file (MEDPAR) contains claims and billing data from inpatient hospitalizations, which are covered under Medicare Part A. The Medicare outpatient file contains claims from outpatient services rendered, which may be delivered at a number of facility types, including hospital outpatient departments, rural health clinics, and outpatient rehabilitation and dialysis facilities. The carrier claims file contains all bills from physicians and other health professionals. Services represented in the carrier file may be delivered at hospitals or office settings. Additional information about providers and facilities is available in the National Cancer Institute hospital file.[121]

3.1.2. Inclusion/exclusion Criteria

For both Aim 1 and Aim 2, the sample of interest was male Medicare beneficiaries diagnosed with primary cancer of the prostate gland. The following inclusion criteria have been used in previous studies of prostate cancer using SEER-Medicare data[122,123] and were reviewed by experts in urology and oncology. For included men, prostate cancer was the first and only cancer diagnosis, and men diagnosed at autopsy or on their death certificate were excluded. No men with end-stage renal disease (ESRD) as the reason for Medicare entitlement were included, nor were men with multiple prostate primary cancer sites. Subjects were at least 65 years old at diagnosis, had one full year of Medicare claims before their diagnosis, and were alive at 12 months post-initial treatment. Additionally, they were continuously enrolled in Medicare Parts A and B (in the form of a FFS plan) from 12 months pre-diagnosis to at least 12 months after initial treatment. Although these restrictions resulted in the exclusion of many men with full cancer diagnosis data in the PEDSF file, complete

Medicare claims data are necessary to characterize surveillance care and secondary treatment.

Men in the analytic sample for Aims 1 and 2 received radical prostatectomy as their initial cancer therapy within 6 months of prostate cancer diagnosis. Eligible surgical procedures as reported in SEER data were radical prostatectomy, total prostatectomy, prostatectomy with resection in continuity with other organs, and prostatectomy not otherwise specified. Men coded in SEER as having received transurethral resection of the prostate, local tumor destruction, local tumor excision, or surgery not otherwise specified were not considered to have received surgery as cancer treatment and were excluded from the analysis, as in these men, cancer is often an incidental finding during surgery for benign disease.[91] Surgery receipt was confirmed through the examination of Medicare claims, and men must have had a record of surgery in both SEER and Medicare data to be included in the sample. Medicare codes used to identify surgery and other treatments are presented in Table 4. Men with SEER-reported initial treatment of watchful waiting were excluded, regardless of any surgical procedures they may have had during the study period. Many men who ultimately receive surgery as treatment for prostate cancer may have initially chosen watchful waiting or active surveillance as their primary therapy.

Pathological rather than clinical disease stage was used to define the sample as the pathologic disease stage has more weight than the clinical stage in determining the course of future surveillance and treatments for patients who receive radical prostatectomy. Pathological disease stage was used as an additional inclusion criterion. Men with metastatic disease at diagnosis, missing pathological disease stage, pT4 disease, or metastases in regional lymph nodes were excluded, leaving only those with pT2 and pT3 (that is, clinically localized) disease and no nodal disease.

Table 4. Billing Codes Used to Identify Relevant Procedures

	ICD-9	CPT/HCPCS
PSA testing		84152-84154, G0103
Radical prostatectomy	60.4, 60.5, 60.6x	55810, 55812, 55815, 55840, 55842, 55845, 00865, 55866
External beam radiation therapy*	92.24, 92.26	77301, 77305, 77310, 77315, 77321, 77371-77373, 77380, 77381, 77401, 77403-77409, 77411-77414, 77416, 77418, 77422, 77423, 77520, 77522, 77523, 77525, 77526, 0073T, G0178
Brachytherapy and other radiation therapy	92.20, 92.21, 92.22, 92.25, 92.23, 92.27, 92.28, 92.29	55859, 55860, 55862, 55865, 55875, 76873, 77470, 77750-77799, 79005-79999, C1164, C1174, C1325, C1350, C1700, C1701, C1702, C1715-C1720, C1728, C1790-C1806, C2638, C2639, C2640, C2641, G0256, G0261, Q3001
Hormone therapy	62.3, 62.4x	54520, 54522, 54530, 54535, 54690, J1050, J1051, J1950, J3315, S0175, J9000-J9999
Chemotherapy	99.25, V58.1x, V66.2, V67.2	96400-96549, Q0083-Q0085

*These codes capture both salvage and adjuvant radiation therapy; the distinction between the two is made by examining treatment timing.

Notes: ICD-9: International Classification of Diseases, 9th Revision; CPT: Current Procedural Terminology; HCPCS: Healthcare Common Procedure Coding System; PSA: Prostate-specific Antigen

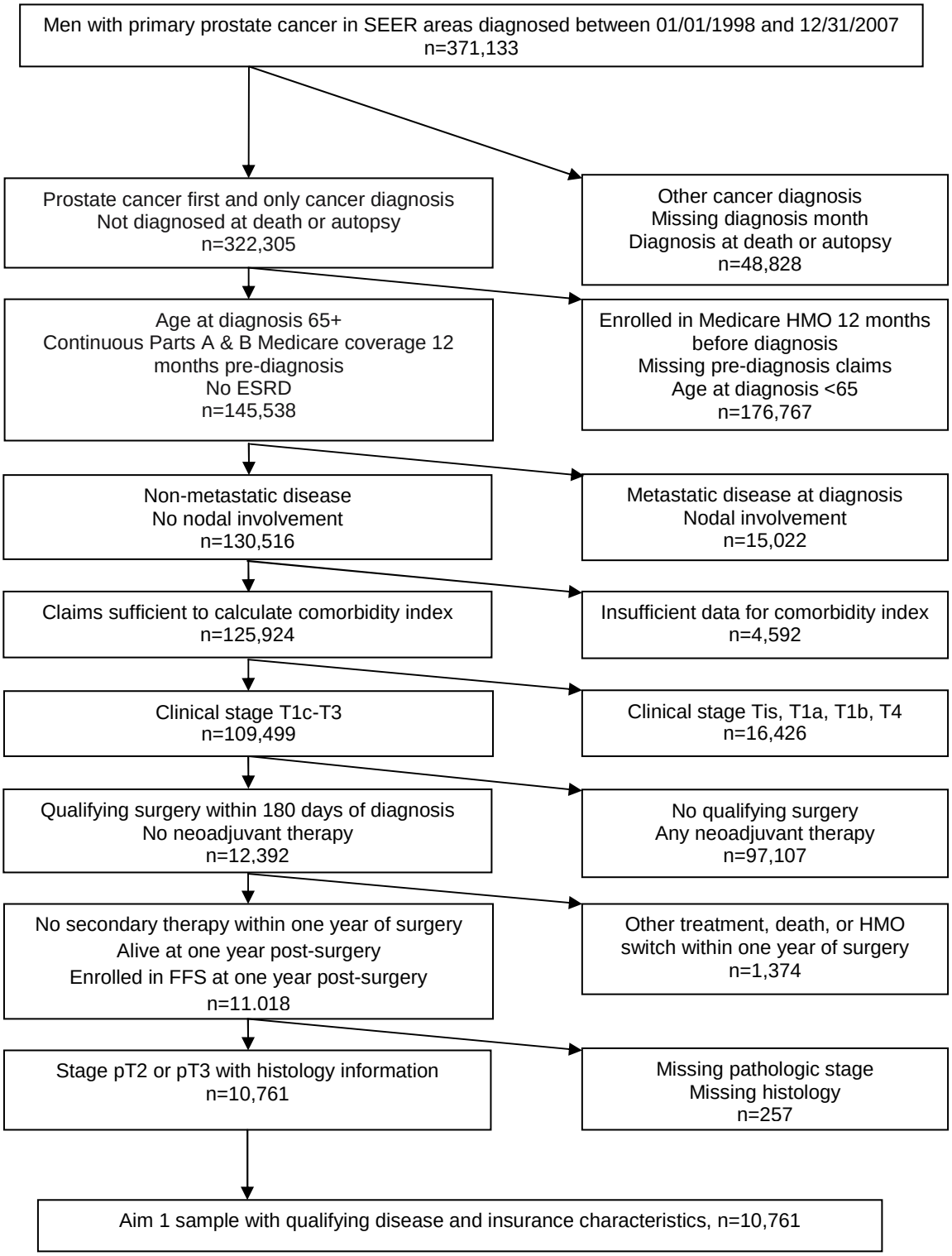
For Aims 1 and 2, adjuvant radiation therapy (ART) (as opposed to salvage or palliative radiation therapy) was defined as radiation therapy initiated within 180 days of surgery. As Aim 1 dealt with the period of surveillance following surgery, men were

excluded if they had any claim for brachytherapy, hormone therapy (surgical or medical), or chemotherapy within one year of surgery if they received surgery alone or within one year of the final radiation therapy treatment if they received surgery with ART. Radiation therapy was considered adjuvant rather than salvage if it was initiated within 6 months of surgery. Initiation of an additional therapy (brachytherapy, hormone therapy, or chemotherapy) was considered to mark a shift in the disease course from surveillance to active treatment, and PSA tests received following this shift may not have the same interpretation as PSA tests received during the surveillance period. Men were followed until death, a switch to an HMO plan, disease recurrence (marked by initiation of secondary treatment), or the end of the data period (December 31, 2009). The final sample size for Aim 1 was 10,761.

Figures 1 and 2 summarize these inclusion and exclusion criteria. For Aim 1, men were diagnosed with prostate cancer between January 1, 1998 and December 31, 2007, with follow-up through Medicare claims available through December 31, 2009. For Aim 2, men were diagnosed with prostate cancer between January 1, 2000 and December 31, 2007. Follow-up claims data were available for these men through December 31, 2009.

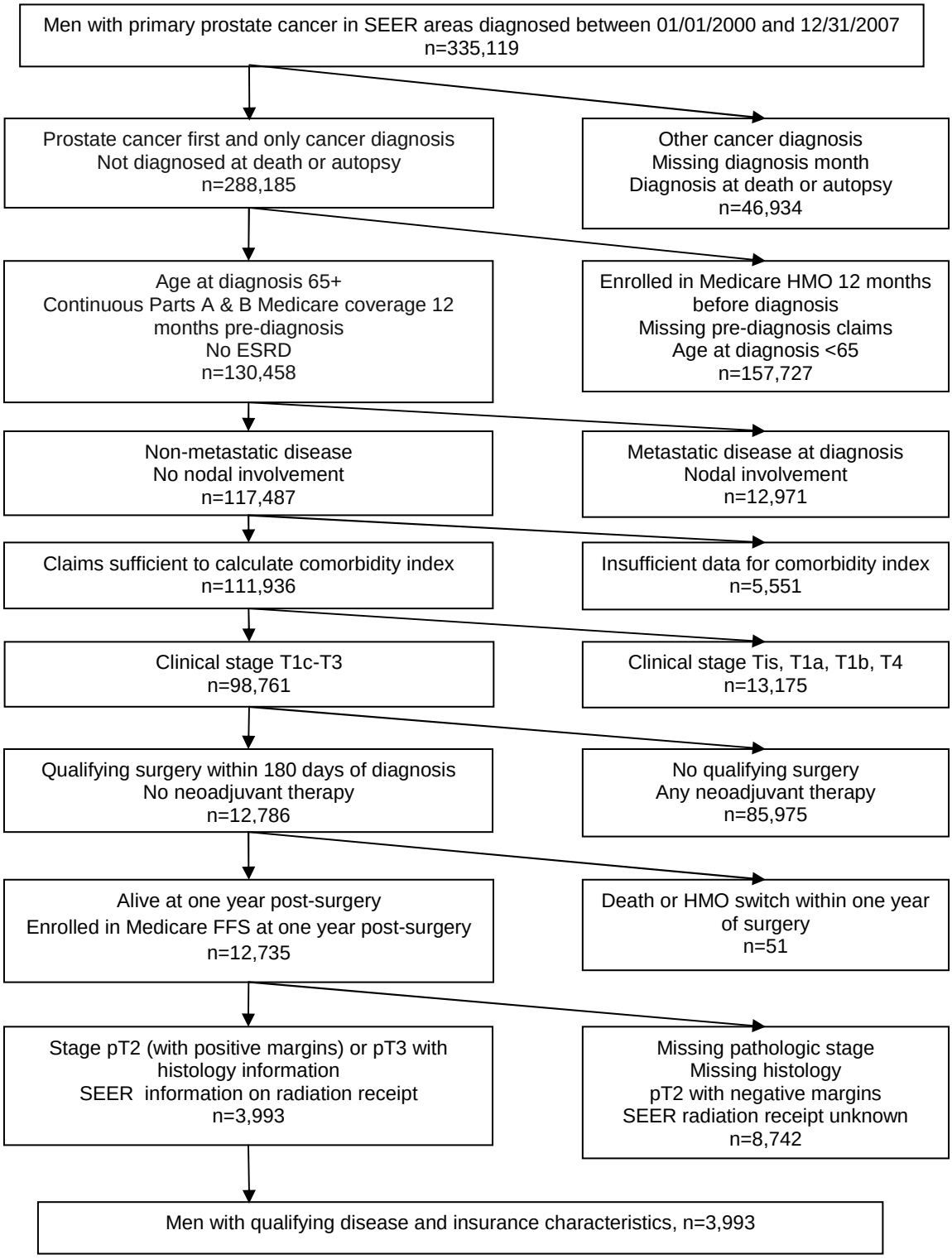
Men included in the Aim 2 sample could have received adjuvant or salvage hormonal therapy or chemotherapy in addition to surgery and any radiation procedures as the goal of this aim was to validate records of radiation receipt rather than document survival or follow-up care for a cohort of men receiving a specific treatment. Additionally, as adjuvant radiation is only recommended for consideration in men with pT2 disease with positive surgical margins or pT3 disease, men with pT2 disease and negative surgical margins were excluded. This resulted in a final sample size of 3,993.

Figure 1. Sample Counts for Included and Excluded Observations, Aim 1



Note: SEER: Surveillance, Epidemiology and End Results; HMO: Health maintenance organization; ESRD: End stage renal disease; FFS: Fee-for-service

Figure 2. Sample Counts for Included and Excluded Observations, Aim 2



Note: SEER: Surveillance, Epidemiology and End Results; HMO: Health maintenance organization; ESRD: End stage renal disease; FFS: Fee-for-service

3.1.3. Dependent, Key Independent, and Control Variables

This section presents an overview of the dependent and independent variables. Dependent variables and key independent variables are presented in Table 5 by aim. I discuss below how each was created and used in the analysis. The control variables used in Aims 1 and 2 are summarized in Tables 6 and 7. See Chapter 4 and Chapter 5 for a discussion of the values taken by each variable along with tables of summary statistics.

Table 5. Dependent and Key Independent Variables, by Aim

Aim	**Variable**	**Potential values**	**Source**
Dependent Variables			
Aim 1	Indicator of receipt of PSA surveillance test	0, 1	Claims
Aim 2	Match between SEER and Medicare on adjuvant radiation receipt	0, 1	PEDSF, Claims
Key Independent Variables			
Aim 1	Years past primary treatment	Year 1, 2, 3, 4, 5, 6+ indicators	Claims
Aim 1	Race/ethnicity	Non-Hispanic white, non-Hispanic black, Hispanic, unknown/other	PEDSF
Aim 2	Tumor differentiation	Well/moderately differentiated, poorly differentiated	PEDSF
Aim 2	Pathologic disease stage	pT2, pT3	PEDSF

Note: PEDSF: Patient Entitlement and Diagnosis Summary File; PSA: Prostate-specific antigen; SEER: Surveillance, Epidemiology, and End Results

Dependent Variables

For Aim 1, the primary dependent variable of interest was a binary indicator of whether a man received a surveillance PSA test in a given year following treatment. As strict adherence to surveillance guidelines would require PSA testing every 6 months, an

alternative measure of testing receipt was defined using a binary variable indicating whether a patient received at least one test in a given 6-month interval.

I examined claims data to find all instances of PSA testing beginning 60 days following surgery for men receiving surgery alone as a primary treatment and 60 days following the last radiation therapy treatment for men receiving surgery with ART. All claims containing a PSA test within five days of a previous PSA test were considered to be duplicate claims and not counted toward the annual test total. All PSA test claims occurring on the date of or after the initiation of secondary therapy were excluded. Secondary therapy procedures included salvage radiation therapy (more than 6 months after surgery), orchiectomy, androgen deprivation therapy, brachytherapy, and chemotherapy. Men must have had at least one full year of data following treatment to be included in the sample.

I identified relevant procedures and claims, current and historic billing codes (Table 4) from journal articles,[123,124] SEER-Medicare training information,[125] International Classification of Diseases, 9th edition (ICD-9) codebooks,[126,127] a Current Procedural Terminology (CPT) codebook,[128] and online Healthcare Common Procedure Coding System (HCPCS) documentation.[129] I extracted all claims with the relevant billing codes for men meeting the inclusion criteria detailed in Figures 1 and 2. Although revenue center codes are included in Medicare billing information and are often used to identify radiation procedures,[34] there is no way to distinguish external beam radiation therapy from brachytherapy using revenue center codes alone. For this reason, I did not use revenue center codes as a way to identify relevant claims. Additionally, as I was interested in receipt of radiation therapy procedures rather than planning, I did not include codes related to treatment planning or management. I extracted all claims from 30 days prior to diagnosis until HMO enrollment, death, or December 31, 2009.

Although PSA tests are coded differently for diagnostic/screening versus surveillance purposes, I included claims for PSA tests with either code to capture full disease surveillance. As all PSA tests for men in my sample occurred after a prostate cancer diagnosis, any tests with a diagnostic billing code were considered miscoded surveillance tests.

For Aim 2, the dependent variable was a binary variable indicating whether SEER and Medicare agreed in terms of ART receipt. I first constructed two separate binary variables, one for documentation of ART receipt in SEER and one for documentation of ART receipt in Medicare claims. The dependent variable used in the analysis was equal to one if the SEER and Medicare binary variables matched and zero otherwise. There were two ways in which the records for an individual could not agree: either by having documentation of ART in SEER but not Medicare, or by having documentation of ART in Medicare but not SEER.

SEER data contain a radiation therapy variable describing the type of radiation therapy administered as a first course of treatment.[130] Radiation therapy is coded as none, received (by type of radiation therapy), refused, recommended, or unknown, and the possible types of radiation therapy are beam radiation, radioactive implants, radioisotopes, a combination of beam and other radiation therapy, and radiation therapy NOS. I created an indicator of ART receipt using this treatment variable. Men with combination therapy and radiation therapy NOS were considered to have received ART; men for whom radiation therapy was recommended (but receipt was unknown) and men who refused were considered not to have received radiation. Men who received radioactive implants and radioisotopes were not considered to have received ART these modalities are not recommended adjuvant to radical prostatectomy.[22] Men with unknown radiation therapy receipt were excluded.

The Medicare ART receipt variable was constructed using claims data. Men with claims for external beam radiation therapy beginning within 6 months of surgery were given a value of one for the Medicare radiation therapy receipt binary variable. The variable was equal to zero for all other men. Radiation therapy delivered outside of the 180-day window after surgery was also captured in Medicare claims. Radiation therapy in this setting could be considered salvage (delivered with curative intent in response to disease recurrence) or palliative (delivered in response to symptoms of metastatic disease), but it is not the intent of this research to distinguish between the two. Regardless, men who received any radiation therapy outside the 180 day window from surgery did not receive ART. The dependent variable for the Aim 2 analysis was constructed to indicate whether or not there was a match in the receipt of ART across SEER and Medicare records for each individual.

Key Independent Variables, Aim 1

Key independent variables for Aim 1 were the time elapsed since treatment (measured in years) and patient race/ethnicity. Each observation captured a single year for an individual, and only complete years of data were included in the sample. That is, a man with 6 and a half years between surgery and death is represented by 6 observations in the sample. The year was measured as an indicator of whether the observation covered the first, second, third, fourth, fifth, or sixth or later year. That is, the sixth year and following were assumed to have the same effect on the likelihood of receiving a PSA test.

The SEER version of race/ethnicity was used to measure patient race/ethnicity. Medicare claims also report race/ethnicity, but it is believed that the SEER data are superior, due in part to the use of a Spanish-surname algorithm.[131] Race/ethnicity was coded as non-Hispanic white, non-Hispanic black, Hispanic, and other/unknown. The

largest race/ethnicity categories among the last group were Japanese (21%), other Asian or Pacific Islander (39%), and unknown race/ethnicity (15%).

Key Independent Variables, Aim 2

The decision to initiate ART may not be made until after examination of the surgical specimen, so pathologic disease stage and tumor differentiation were examined in the analysis to identify individuals with adverse disease features. Individuals with higher PSA levels, higher Gleason scores, and pT3 disease are those individuals for whom ART is most likely to be recommended, but that recommendation may hinge on surgical findings and may not be well documented in the initial treatment plan. Specific Gleason score and PSA level were not available for all years of data, so a collapsed measure of tumor differentiation based on Gleason score and pathologic disease stage were used as the key independent variables in the Aim 2 analysis.

Control variables, Aim 1

Individual-level measures of age, marital status, tumor characteristics, co-morbidity, and Medicare state buy-in at diagnosis were used to control for the likelihood that an individual would receive a PSA surveillance test in a given year following initial treatment (Table 6). Tumor characteristics included an indicator of pathologic tumor stage (pT2 or pT3, where pT3 tumors are characterized by extraprostatic extension), and tumor histology, which was captured by a binary variable indicating whether the combined Gleason score of the tumor was less than or equal to 7 (well/moderately differentiated) or greater than 7 (poorly differentiated). Comorbidities documented in Medicare claims within the year prior to diagnosis were measured by the National Cancer Institute (NCI) Combined Comorbidity Index, which was developed specifically for use with SEER-Medicare data and includes prostate cancer-specific weights.[132] Medicare state buy-in at diagnosis was used to help control for income, healthcare access, and individual characteristics not otherwise captured. Although this indicator has

previously been used to identify individuals who are dually-eligible for Medicare and Medicaid, a recent paper cast doubt on the adequacy of the buy-in indicator to appropriately identify dually-eligible individuals.[133]

Table 6. Aim 1 Control Variables, Values, and Sources

Variable	Type	Potential Values	Source
Individual-level			
Age at diagnosis	Continuous		PEDSF
Marital status	Binary	Married, not married	PEDSF
Co-morbid conditions, measured by the NCI Combined co-morbidity index	Continuous		Claims
State buy-in at diagnosis	Binary	Yes, No	PEDSF
Pathologic tumor stage	Binary	pT2, pT3	PEDSF
Tumor histology	Binary	Well/moderately or poorly differentiated	PEDSF
Diagnosis year	Categorical	1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007	PEDSF
County-level			
Racial isolation index	Continuous		U.S. Census
Persistent poverty indicator	Binary	Yes, No	ERS, USDA
Population density	Continuous		U.S. Census
Social capital index	Continuous		NRCRD, PSU
Medicare HMO Penetration	Continuous		RTI Spatial Database

Note: PEDSF: Patient Entitlement and Diagnosis Summary File; SEER: Surveillance, Epidemiology, and End Results; PSA: Prostate-specific Antigen; HMO: Health maintenance organization; RTI: Research Triangle Institute; NCI: National Cancer Institute; ERS: Economic Research Service; USDA: United States Department of Agriculture; NRCRD, PSU: Northeast Regional Center for Rural Development, Penn State University

County-level measures of population density,[120] persistent poverty,[134] racial isolation,[135] social capital,[136] and Medicare HMO penetration[120] were included in the models to control for access to care and local practice patterns. These county variables were specific to the last known county in which each individual received a PSA test or

the county in which the individual was diagnosed for those with no record of PSA test receipt. Annual population density (measured as 1,000 individuals per square mile) was used to control for geographic isolation and as a potential measure of access to care. An additional control for access to care was an indicator of persistent poverty for the year 2004, which indicates that at least 20% of the county population had a household income below the poverty level in the last 4 decennial U.S. censuses.[134] A race/ethnicity-specific measure of racial isolation/segregation was included to capture the social support networks available in each individual's community.[135] This measure is based on 2000 U.S. Census data and has been shown to influence receipt of screening mammography in the Medicare population.[137] I also included a measure of community social capital, which may influence an individual's ability to seek and obtain medical care. This 2005 county-level measure is a composite index based on the number of civic and non-profit organizations in county, voter turn-out, and Census return rates.[136] Finally, a county-level measure of the percent of Medicare-eligible beneficiaries participating in an HMO plan was used to control for variations in practice patterns that may be attributable to a managed care spillover effect.[138] This measure was available for the years 2001-2005; the 2001 value was assigned to observations from 1998-2001 and the 2005 value was assigned to observations from 2005-2009.

Control variables, Aim 2

Previous validation studies in the breast cancer literature have found differences in the likelihood of a registry-claims match by age at diagnosis,[94,96] but there is little evidence that other demographic and socioeconomic characteristics affect the likelihood that registry and claims records would agree on ART receipt. However, these characteristics may be related to disease severity as well as the type of treatment received,[68,139,140] so I included age at diagnosis, marital status, and race/ethnicity as control variables. Table 7 presents the full set of control variables.

Table 7. Aim 2 Control Variables, Values, and Sources

Variable	Type	Potential Values	Source
Individual-level			
Age at diagnosis	Continuous		PEDSF
Race/ethnicity	Categorical	Non-Hispanic white, non-Hispanic black, Hispanic, unknown/other	PEDSF
Marital status	Binary	Married, not married	PEDSF
SEER Region	Categorical	San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose, Los Angeles, rural Georgia, Greater California, Kentucky, Louisiana, New Jersey	PEDSF
Community-level			
Medicare HMO Penetration	Continuous		RTI Spatial Database
Hospital-level			
Bed size of surgical facility	Continuous		NCI file
NCI Cancer Center designation	Binary	Yes, No	NCI file
Medical school affiliation	Binary	Yes, No	NCI file
Radiation treatment provided at surgical facility	Binary	Yes, No	NCI file

Note: PEDSF: Patient Entitlement and Diagnosis Summary File; SEER: Surveillance, Epidemiology, and End Results; PSA: Prostate-specific antigen; HMO: Health maintenance organization; RTI: Research Triangle Institute; NCI: National Cancer Institute

Agreement on radiation therapy receipt was found to vary across SEER regions in a previous study of radiation receipt in SEER data,[34] so SEER region at diagnosis was included to control for potential differences in how well different registries capture treatment information. Surgical facility characteristics, particularly bed size and National Cancer Institute (NCI) affiliation (defined as being a clinical or comprehensive designated cancer center) were also hypothesized to affect the type of treatment

received as well as the documentation and reporting of treatments.[96] The surgical facility characteristics were included as control variables rather than the diagnosing facility characteristics as the surgery results may play a larger role in determining the course of future treatment than results from a diagnostic biopsy. NCI affiliation was available only for 2002 and 2005; the 2002 affiliation was used for diagnoses between 2000 and 2003 and the 2005 affiliation was used for diagnoses between 2004 and 2007. Other surgical facility characteristics included in the models were medical school affiliation and the whether the facility provided therapeutic radiology services or not. A facility was classified as affiliated with a medical school if affiliation was major, limited, or graduate-level only. Other than NCI affiliation, all facility level variables were available for 2000-2007.

3.1.2. Aim 3 Data

Cost-utility models require event probabilities, utilities in terms of quality-adjusted life years (QALYs), and costs as inputs. Disease and treatment-related probabilities and utilities came from the peer-reviewed literature. I conducted a PubMed search using the following terms alone and in combination: prostate cancer, cancer, quality of life, utility, cost-effectiveness, cost-utility, QALY, willingness to pay, quality of life, comparative effectiveness, and health-related quality of life. This search process began in May 2011, and was periodically repeated between May and December 2011 to capture any new publications. Additionally, I reviewed the table of contents of new issues of 19 relevant journals to find new publications. Titles and abstracts located through the PubMed searches and table of contents were reviewed to identify articles that contained relevant model inputs. I also reviewed reference lists of relevant articles to identify any additional publications that might contain data relevant to the model. Costs came from the Medicare physician fee schedule[141] and the 2010 *Red Book*.[142] This section provides

information on the methods used to collect these inputs, and Chapter 6 contains tables detailing the input values and distributions.

Probabilities

Results from clinical trials and retrospective series were used to derive transition probabilities for the model. Probabilities associated with biochemical recurrence following radical prostatectomy and biochemical recurrence following ART came from a recent clinical trial.[6] Probabilities for progression from disease recurrence to metastatic disease and progression from hormonally responsive metastatic disease to hormone-refractory disease came from retrospective studies,[4,5,83,143] and biochemical recurrence following salvage radiation therapy (SRT) and survival following hormone-refractory disease were calculated using peer-reviewed risk prediction nomograms.[5,144] Additional probabilities of disease progression following radical prostatectomy, ART, and SRT were derived for subgroups of men with and without positive surgical margins and with and without seminal vesicle invasion. When available, event counts were used to create beta distributions around the base-case probability. If event counts were not presented in the source article, a beta distribution was approximated from a mean and standard deviation.[100] If no distribution information was available, I assumed that the standard deviation was 20% of the base-case value and approximated a beta distribution from this information. All probabilities were converted from annual or multiple year probabilities to quarterly probabilities.[100] The annual probability of death from background causes was obtained from the 2007 U.S. life tables for men.[145]

The probabilities for developing short- and long-term urinary, sexual, and gastrointestinal adverse effects following radical prostatectomy and radiation therapy came from a random-effects meta-analysis conducted by Hayes et al.[112] Short-term adverse events resolved within 3 months of treatment, whereas long-term adverse events persisted from 3 months until death. Following the methods of Elliot et al.,[118] the

probabilities of developing adverse events were considered to be the probability of developing the given adverse event alone and in combination with other adverse events.

Utilities

Substantial research exists on prostate cancer-related quality of life and health states.[146] Titles and abstracts located through the PubMed searches described above were reviewed to identify articles that reported utility values rather than quality of life or functioning scores. Although many instruments are used to evaluate quality of life in prostate cancer patients,[147] few of these instruments generate utility measures, which are essential in construction of a cost-utility model. Many of the articles identified in the initial search were cost-effectiveness or cost-utility studies that referenced utility values from a previous study, so reference lists of relevant articles were reviewed to identify any additional publications.

I identified 30 studies reporting utilities and used them to create a database of prostate cancer-specific utility values containing 289 utility values. Values were categorized as describing a treatment state, adverse event, short-term effect, and/or long-term effect. The quality of each measure and its relevance to the current study were evaluated by examining the population from which the value was elicited, the elicitation technique, the sample size, and the utility scale endpoints. Utilities from scales using anchors other than death and perfect health were excluded. Utility values derived from expert opinion also were excluded unless they were the only ones representing a specific health state. To ensure the consistency of the evaluated outcomes, studies were excluded if cancer patients were asked to evaluate the utility of their current health state rather than a standard health state description.

Seventeen of the studies presenting prostate cancer-related utilities involved utilities related to metastatic disease. Of these 17 studies, seven met the inclusion criteria described above, however 3 studies appeared to use the same data set, bringing

the total number of studies with useful utility data to 5.[113,115,148-150] Two of these 5 studies reported more than one utility measure.[149,150] Since the model had two metastatic disease states, utilities were separated by whether or not the disease was responsive to hormonal therapy (specifically, leuprolide). In cases where the authors did not specifically state the level of disease advancement, the disease description used in the utility exercise was used to properly categorize the utility. This process resulted in a final group of 4 estimates from 2 studies for the utility of living with metastatic prostate cancer responsive to hormonal therapy[149,150] and 7 utility estimates from 5 studies for the utility of living with metastatic prostate cancer that is no longer hormonally responsive.[113,115,148-150] For hormonally responsive disease, the utility value mean and standard deviation were determined by examining the means, standard deviations (where available), and interquartile ranges (where available) to derive a single mean and standard deviation reflective of the ranges reported in the two studies. For metastatic disease no longer responsive to hormonal therapy, the utility value mean and standard deviation were taken from Stewart et al.[148] as this study focused specifically on the preferences of men aged 60 and older, used the standard gamble technique (which, all else equal, is preferred to the time trade off technique used in the other studies for preference elicitation[102]), and falls in the middle of the range of utilities reported in the five studies.

The utilities associated with living with adverse effects related to treatment were taken from Stewart et al.[148] In contrast to other utility studies that examine the utilities of adverse effects separately, Stewart et al. elicited utilities for adverse effects singularly and in combination. These combinations are essential for evaluating health states following prostate cancer treatment, as individuals may experience multiple treatment-related adverse effects, and no model exists to accurately predict joint health state utilities from the component single health state utilities.[151]

Costs

With the exception of drug costs, all cost data for the analysis were derived from established Medicare fee schedules. Costs were from the calendar year 2011 fee schedule,[141] which is based on Healthcare Common Procedure Coding System (HCPCS) codes. As the difference in salvage and adjuvant radiation therapy is only in the timing of the treatment rather than the dosage or administration, both arms of the model incorporate essentially the same costs. The model did not include costs associated with radical prostatectomy or surgical follow-up, as all individuals experienced this procedure prior to the beginning of the model. Included costs are those costs associated with radiation therapy administration and follow-up and management of metastatic disease.

The Centers for Medicare and Medicaid Services (CMS) provides information on both the national payment amount and Part B carrier-specific payment amounts. The national payment amount was used in the base-case analysis, and the carrier-specific amounts were used to create a distribution for probabilistic analysis. Input Analyzer (Arena Version 13.9, Rockwell Automation, Inc., Wexford, PA) was used to analyze the entire set of payment amounts and create distributions to best fit the data.

Metastatic disease was assumed to be initially treated with gonadotropin-releasing hormone agonist (leuprolide) rather than orchiectomy, and hormone-refractory disease was assumed to be treated with bicalutamide. Drug prices were obtained from the 2010 edition of the *Red Book*[142] and adjusted for inflation using the medical care component of the Consumer Price Index.[152] All individuals were assumed to receive semi-annual PSA tests regardless of timing of radiation so this was cost excluded. As the adverse effects included in the model were considered to be minor rather than requiring substantial medical intervention, there were no additional costs associated with adverse effects.

3.2. Analytical Methods

3.2.1. Aim 1

This aim examined PSA surveillance in men diagnosed with prostate cancer between January 1, 1998 and December 31, 2007. The use of PSA surveillance testing was characterized as an annual binary indicator of whether a man received at least one test during a given year. The 1997 National Comprehensive Cancer Network (NCCN) Guidelines called for PSA testing every 6 months over the first 5 years and annually thereafter for men who received potentially curative initial therapy, which includes radical prostatectomy and radiation therapy.[66] In the revised 2007 Guidelines, the testing interval for the first 5 years changed from every 6 months to every 6 to 12 months.[67] Additional definitions of surveillance, specifically the receipt of at least one test in a 6-month period and at least one test in a 9-month period, were examined and compared to assess the sensitivity of the results to different measures of surveillance.

I first used descriptive statistics and bivariate statistical tests to examine the data. To examine whether there might be differences in men who always received an annual test and those who did not, I calculated and compared summary measures of demographic, socioeconomic, and tumor characteristics for men who received at least one test per year and men who did not receive at least one test per year over the first five years following treatment. In addition, I calculated unadjusted associations between selected patient characteristics and PSA test receipt using bivariate statistical tests such as the t-test and Chi-square test.[153] Specifically, I tested whether receiving at least one PSA test per year was significantly different across racial groups and initial treatment types. I used a 0.05 level of significance to determine statistical significance.[154]

Logistic models, estimated using a generalized estimating equations (GEE)-based approach, were used to evaluate the influence of covariates on whether an individual received a PSA test in a given year. Analysis was conducted at the person –

year level (or the person-period level for the 6-month and 9-month models). I tested functional forms for independent variables (log and polynomial specifications as well as continuous versus categorical specifications) as well as the appropriate use of interaction terms by using Wald test statistics[154] and the quasi-likelihood under the independence model information criterion (QIC).[155] I used Stata version 10.0 (Stata Corporation, College Station, Texas) and SAS version 9.1 (SAS Institute, Inc., Cary, North Carolina) to compile the data. All statistical analyses were conducted in Stata.

3.2.2. Aim 2

In this aim I compared the agreement between receipt of ART as coded in SEER and billing codes included on Medicare claims. The sample for this aim included men diagnosed with prostate cancer between January 1, 2000 and December 31, 2007 who received radical prostatectomy as initial treatment.

For the initial descriptive analysis I calculated the percentage of men who received ART according to SEER records. I calculated unadjusted associations between selected patient characteristics and ART receipt using bivariate statistical tests such as the t-test and Chi-square test.[153] I then calculated rates of agreement across the two data sources by registry, year of diagnosis, and patient characteristics. As there may be differences between men who have a record of ART receipt in one source but not the other, I compared summary characteristics across three groups of men: those who had a record of ART in both sources, those who had a record of ART in SEER but not Medicare, and those who had a record of ART in Medicare but not SEER. All statistical tests were conducted using a significance level of 0.05.[154]

The main analysis for this aim consisted of a logistic regression model.[153] The dependent variable was an indicator of agreement between SEER and Medicare on receipt of ART. This agreement was modeled as a function of individual and hospital characteristics described previously. I tested functional forms for independent variables

(log and polynomial specifications and continuous versus categorical specifications) as well as the appropriate use of interaction terms by using Wald test statistics and examining changes in the likelihood ratio test statistic.[154] All statistical tests used a significance level of 0.05. Observations were clustered at the surgical facility level to help control for correlation in observations from a single institution.[154]

I compiled the data both in SAS, version 9.1 (SAS, Cary, NC) and Stata, version 10 (StataCorp, College Station, TX). I performed all data analysis in Stata.

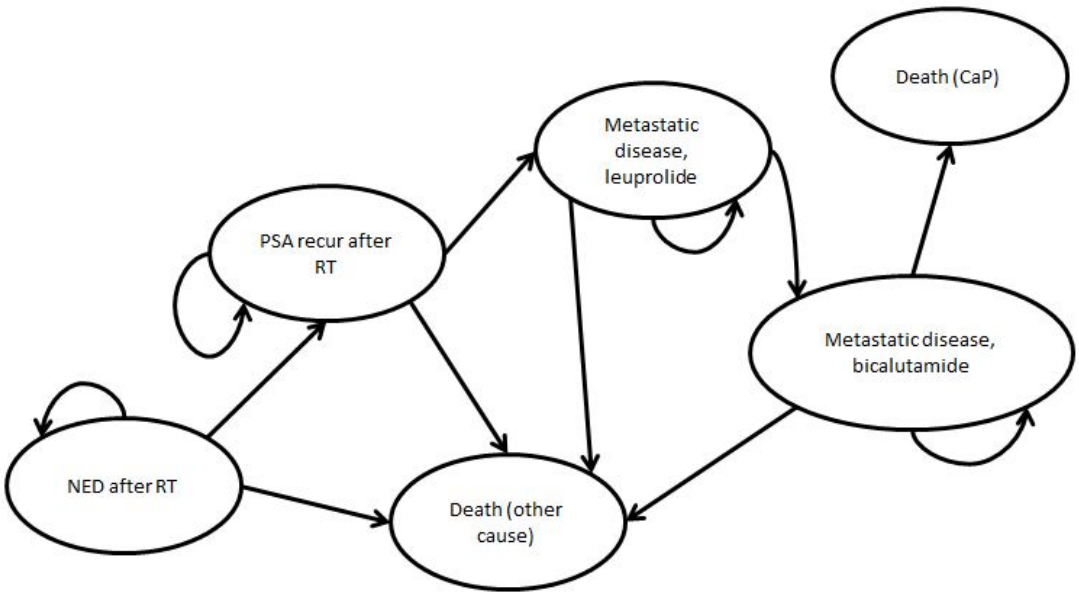
3.2.3. Aim 3

For the Aim 3 analysis I constructed a cohort Markov model to estimate the cost-utility of the current wait and see approach to salvage radiation therapy compared to an alternative policy of ART within six months of prostatectomy for all qualifying patients. In addition to calculating the cost and utility of each approach, I also estimated the proportions of the sample who would experience disease recurrence, develop metastatic disease, and die of prostate cancer under each alternative. Each policy was modeled separately, and the model outputs were compared to identify the superior strategy. All modeling and analyses were performed in TreeAge Pro 2011 (TreeAge Software, Inc., Williamstown, MA).

In the model of outcomes following ART, all individuals begin in the state "NED (no evidence of disease) after RT" (Figure 3). In each period of the model, defined as three months, individuals could remain in their current disease state or move from their current disease state to a new one with different associated costs and utilities.[102] Movement from one state to another was determined by the transition probabilities defined previously. In each three month period, individuals made one transition (represented by a single arrow) through the model. In this way, all individuals moved through the model until they ended in an absorbing state, that is, one that does not allow outward movement. In this model, individuals eventually cycled into the absorbing states

or death from prostate cancer (“Death, CaP”) or death from other causes (“Death, other cause”). Individuals could transition into death from other causes from any state in the model (other than death from prostate cancer) at any time, while individuals could only transition to death from prostate cancer after developing metastatic disease. The model for the wait and see approach is similar, but individuals begin in a state of “no evidence of disease following radical prostatectomy” and must transition through “PSA recurrence after radical prostatectomy” before entering the “NED after RT” state as depicted in Figure 3.

Figure 3. Markov Model for ART Approach



Note: NED: No evidence of disease; RT: Radiation therapy; PSA: Prostate-specific antigen; CaP: Prostate cancer

Each state in the model and the associated events had costs and utilities, which contributed to the overall cost and utility of each approach. All costs and utilities occurring in the future were discounted at 3% per year to account for the time value of money and utility.[102,156] I populated the model from the payer perspective (Medicare) over the time horizon from initial treatment to death. In contrast to a societal perspective

that includes all costs, the payer perspective does not include costs associated with productivity loss and patient time.[99]

I used the model to calculate the total cost and the total utility associated with the ART approach and the total cost and the total utility associated with the wait and see approach. In addition, the proportion of the cohort experiencing disease recurrence, receiving radiation therapy, developing metastatic disease, and dying from prostate cancer were calculated for each alternative. These cost and utility totals were used to calculate the incremental cost-effectiveness ratio (ICER), as demonstrated by:

$$ICER = (Cost_{(adjuvant)} - Cost_{(wait\ and\ see)})/(Benefit_{(adjuvant)} - Benefit_{(wait\ and\ see)})$$

The ICER either will be positive or negative, and the interpretation of the ICER can most easily be seen by plotting the incremental costs (y-axis) and benefits (x-axis) on an x-y axis (called the incremental cost-effectiveness plane). Incremental cost and effectiveness are plotted as a point, and ICER is the slope of the line from the origin to the point. When the point estimate ICER falls in northwest or southeast quadrants, one alternative is clearly superior to the other, that is, it costs less and is more effective than the other.[102] Points (and therefore ICER values) falling in northeast or southwest quadrants represent alternatives with a trade-off between cost and effectiveness. The standard practice is to establish a threshold for the maximum willingness to pay (WTP) per QALY.[102] The slope of a line running through the origin of the x-y axis represents this WTP threshold. An ICER above the threshold indicates the superiority of the wait and see approach, whereas an ICER below the threshold indicates the superiority of ART. Generally, in the U.S., an intervention or program is considered cost-effective if the ICER is less than $50,000 per QALY.[103]

Clearly, a single estimate of the ICER is insufficient for drawing conclusions about the relative costs and benefits of the two approaches to radiation therapy. Although a single estimate for each parameter was chosen for the base-case scenario,

one-way and probabilistic sensitivity analyses were used to test the sensitivity of the results to changes in each parameter.[102]

In one-way sensitivity analyses, one parameter at a time was varied over its range of plausible values to determine how much influence that single parameter had on the ICER.[102] Parameters that have a large influence on the ICER, particularly ones that cause the ICER to move from one quadrant to another, indicate areas in which more information would be most valuable. That is, narrowing down the range of values that parameter might take would lead to a more concise estimate of each alternative's relative value.[102]

In the probabilistic sensitivity analysis, all parameters varied simultaneously.[102] Whereas the one-way sensitivity analysis requires only a range for each parameter, the probabilistic sensitivity analysis requires both a range and a defined distribution.[102] All probabilities are estimated from a binomial proportion, thus beta distributions were assumed.[100] The distributions for the Medicare cost parameters were created from the source data,[141] which indicated that the lognormal and gamma distributions were the best fit. The use of these distributions is supported by the skewed nature of cost data.[100] The 2010 *Red Book* provided 8 prices for bicalutamide and 4 prices for leuprolide,[142] which were used to calculate means and standard deviations. The method of moments approach was then used to create gamma distributions from the means and standard deviations.[100]

The probabilistic sensitivity analysis used a Monte Carlo simulation of 1,000 iterations which selected the values of parameters from the assigned distributions for a cohort moving through the model. The output of the probabilistic sensitivity analysis is 1,000 ICERs, which can be interpreted as the range of potential outcomes.[102]

The resulting ICERs are plotted on the x-y axis and interpreted as described above. Multiple ICERs allow for the calculation of the percentage of ICERs falling in

each quadrant. If all ICERs fall in a single quadrant, then it can be said with some certainty that the true value lies in that quadrant, provided the model is comprehensive and correctly constructed. It is more likely that the ICERs fall in multiple quadrants, or that they fall in the northeast or southwest quadrants, where the determination of the superior treatment depends on how much the payer, in this case, Medicare, is willing to pay per QALY gained.

Results from the probabilistic sensitivity analysis results also were used to plot a cost-effectiveness acceptability curve (CEAC). The CEAC shows the probability that one intervention is more cost-effective than its comparator over a range of WTP per QALY thresholds.[102] For a given threshold, the CEAC indicates the probability that implementing the intervention would be the "right" choice, that is, that the cost per QALY gained would be equal to or below the WTP per QALY gained. The inverse of this probability is the likelihood that the intervention would be the wrong choice.[102] Plotting the CEAC requires the calculation of the incremental net benefit (INB) for each iteration of the Monte Carlo simulation, where the INB is defined as:

$$INB = \lambda*(Benefit_{(adjuvant)} - Benefit_{(wait\ and\ see)}) - (Cost_{(adjuvant)} - Cost_{(wait\ and\ see)})$$

and λ is the societal WTP for a QALY.[157] In this case, if the INB is positive, the ART approach offers a greater net benefit. If the INB is negative, the wait and see approach offers a greater net benefit. For a range of λ values, the CEAC represents the proportion of iterations in which the INB is positive.[100]

In scenario analyses, cohort characteristics were changed to evaluate outcomes for men with different disease characteristics than those men represented by the base-case. In contrast to the base-case, in which the probability of receiving SRT at disease recurrence was constant over time at 0.75, I created a scenario in which the probability of receiving SRT upon disease recurrence following radical prostatectomy was assumed to be 0.75 for recurrences in the first two years following surgery, 0.50 for recurrences in

years 3-4, and 0.25 thereafter. In an additional scenario to evaluate the effect of increasing PSA values over time since radical prostatectomy, PSA level at initiation of SRT was 0.5 ng/ml for recurrences in the first two years following surgery, 1 ng/ml in years 3-4, and 1.5 ng/ml in year 5 and beyond. Scenario analyses also evaluated outcomes for four groups: men with and without positive surgical margins and with and without seminal vesicle invasion.

4. USE OF PROSTATE-SPECIFIC ANTIGEN TESTING AS A DISEASE SURVEILLANCE TOOL FOLLOWING RADICAL PROSTATECTOMY

4.1. Introduction

Survivors of prostate cancer comprise by far the largest proportion of male cancer survivors (41%).[47] Nearly half of men diagnosed in 2002 received radical prostatectomy, making it the most common form of curative treatment overall and in all age groups except men ages 75 and older.[18] Approximately one-quarter to one-third of patients treated with radical prostatectomy for clinically localized prostate cancer will experience disease recurrence.[1,2] Detectable or rising prostate-specific antigen (PSA) levels after prostate cancer treatment are often the first indicator of recurrent disease, and an early diagnosis of treatment failure can facilitate initiation of potentially curative salvage therapy.[61] PSA surveillance is a cornerstone of prostate cancer survivorship care, since patients with a biochemical recurrence (marked by rising PSA levels) have no associated symptoms. If left untreated, biochemical recurrence can progress to radiographically detectable, incurable, and often symptomatic metastatic disease, with a median time from detectable PSA to distant metastasis of 8 years.[4]

PSA values over time, along with tumor characteristics and time elapsed from treatment to detectable PSA, are important predictors of local versus distant recurrence and help to determine the choice of secondary therapy, especially for patients initially treated with radical prostatectomy.[4,5] Patients receiving salvage radiation therapy after biochemical recurrence appear to have a survival benefit compared to those who do not receive salvage radiation therapy.[82] Furthermore, the effectiveness of post-

prostatectomy salvage radiation in achieving disease control appears to be greatest among patients who receive it at lower PSA levels, typically shortly after detection of recurrent disease.[5] Given the frequency of biochemical recurrence after definitive surgical therapy, the availability of potentially curative salvage treatment, and the above-outlined apparent benefits of early detection of recurrence, appropriate post-treatment surveillance is essential for the large number of prostate cancer patients who receive prostatectomy. The 1997 National Comprehensive Cancer Network (NCCN) Guidelines called for PSA testing every 6 months over the first 5 years and annually thereafter for men who received potentially curative initial therapy, which includes radical prostatectomy and radiation therapy.[66] In the revised 2007 Guidelines, the testing interval for the first 5 years changed from every 6 months to every 6 to 12 months.[67]

Although post-treatment surveillance guidelines exist,[22] little research has been done to document the patterns of care, surveillance, and health services utilization of prostate cancer survivors, particularly in contrast to other common malignancies. Breast[48] and colorectal[49,50] cancer treatment guidelines contain guidance for post-treatment disease surveillance. The use of surveillance colonoscopy after colorectal cancer diagnosis and treatment has been well-documented in multiple populations,[51-54] as has the use of mammography after breast cancer diagnosis and treatment.[55-57] Evidence is lacking, however, regarding the extent to which men actually receive recommended PSA surveillance after initial treatment for prostate cancer with radical prostatectomy.

This paucity of research on follow-up surveillance in prostate cancer survivors is surprising as there are demonstrated racial and geographic differences in prostate cancer treatment and mortality.[68,69] The only study to measure PSA surveillance testing patterns examined men diagnosed more than 20 years ago who received radical prostatectomy, radiation therapy, or active surveillance as initial treatment.[70] In this

small, community-based cohort study of patients diagnosed with prostate cancer between 1991 and 1992 receiving treatment in New Haven and Hartford, Connecticut, the proportion of men who did not receive a PSA test following prostate cancer diagnosis ranged from 22% to 29% in any given year after diagnosis.[70] Fewer than half of men (45%) received at least one test each year during the entire follow-up period, which ranged from one to 9 years. Testing frequency varied with type of initial treatment, race, age, and time since diagnosis.

PSA surveillance may be especially important in groups of men facing higher disease recurrence risk. As a consequence of documented cancer treatment disparities, racial and ethnic minorities, in particular African-American men, who may present with more advanced disease, have more frequent disease recurrence and shorter disease-free survival times.[68,69] This research seeks to document PSA surveillance patterns in men treated with radical prostatectomy for NCCN-defined intermediate-risk and high-risk prostate cancer (see Chapter 2 for risk group definitions) and to identify groups potentially at risk for not receiving follow-up care in accordance with treatment guidelines.

4.2. Methods

4.2.1. Data

Data were obtained from the linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database.[158] SEER data are commonly used to describe trends in cancer diagnosis, treatment, and mortality in the U.S.,[16,69] and the linked SEER-Medicare data are frequently used to examine treatment patterns in prostate cancer.[68,123,139,159,160] The SEER program of cancer registries collects population-based data on all incident cancer cases among residents of the 17 participating reporting areas and is considered to be representative of the U.S. population. Twenty-eight percent of the U.S. population is covered by the SEER registries, which collect information on

patient demographics (including residence at first cancer diagnosis), cancer site, extent of disease, tumor characteristics, initial treatment, and vital status follow-up.[119] Medicare is the primary health insurance provider for 97% of the U.S. population aged 65 and older, and claims are available for Medicare beneficiaries participating in fee for service (FFS) plans (85% of all beneficiaries). Medicare claims are not available for Medicare participants enrolled in health maintenance organization (HMO) plans. HMO penetration rates vary substantially across SEER reporting areas, with California having the highest HMO penetration at 38%.[90] The proportion of Medicare beneficiaries in SEER areas enrolled in HMOs is greater than the nationwide proportion enrolled in HMOs, but this difference has decreased over time.[90] Nationwide, the proportion of Medicare beneficiaries participating in HMO plans averaged 13% from 2001 to 2005, and 18% of Medicare beneficiaries in SEER areas participated in HMO plans over the same time period.[120]

County-level contextual data were obtained from the RTI International Spatial Impact Factor Data, which includes public-use data from a variety of sources, including the U.S. Census, the Centers for Medicare and Medicaid Services, and the U.S. Department of Agriculture Economic Research Service.[120] These data were linked to SEER-Medicare records by county and year (when measures were available for multiple years) and were included in this analysis to help control for factors that may affect access to and utilization of care that are not captured in the SEER-Medicare data.

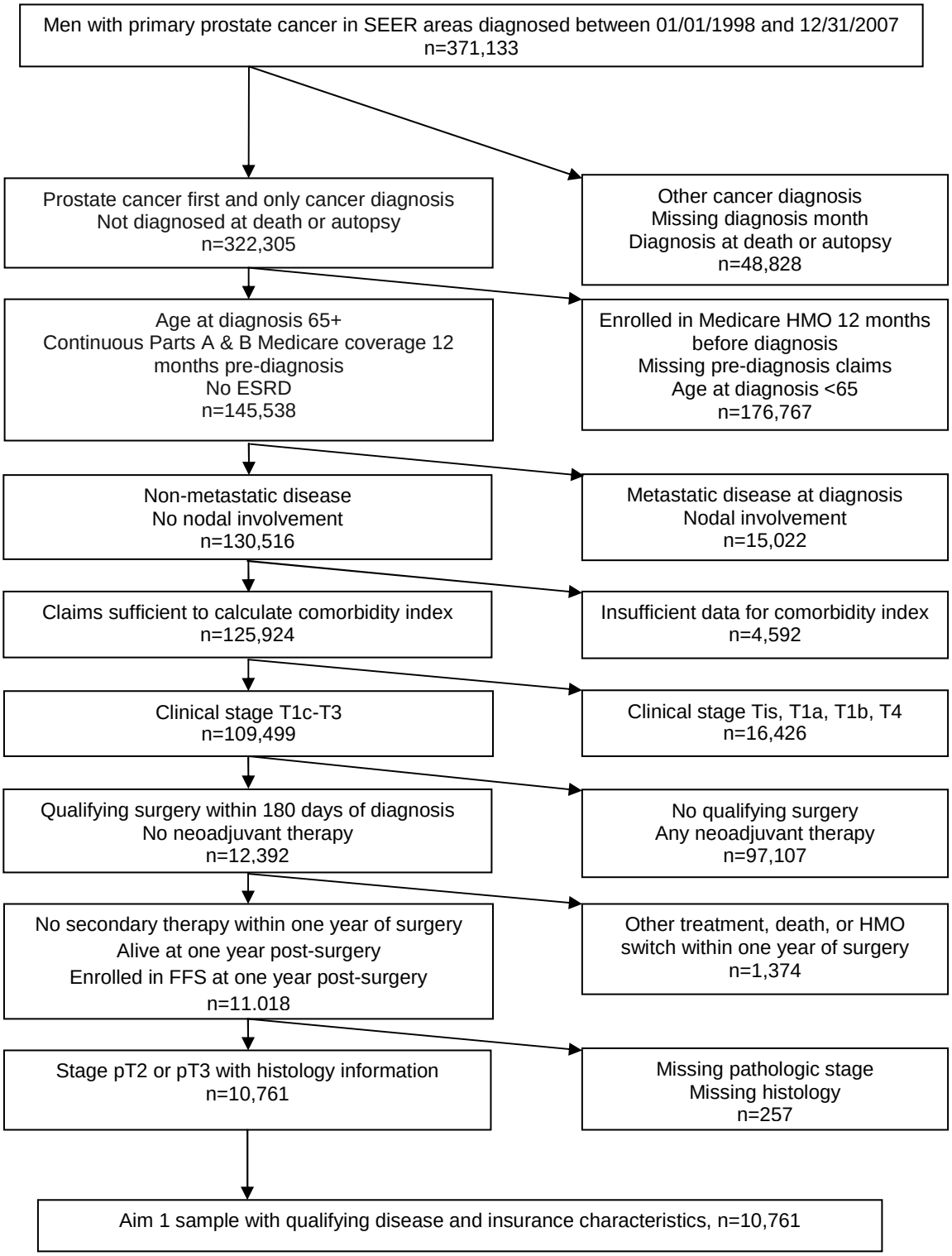
4.2.2. Study Population

Men eligible for this study satisfied the following inclusion criteria, which have been used in previous studies of prostate cancer using SEER-Medicare data[122,123] and were reviewed by experts in urology and oncology. To be eligible for inclusion, men must have received a prostate cancer diagnosis between January 1, 1998 and December 31, 2007 (Figure 4). Medicare claims for these men were available through December 31,

2009. Cases were limited to men for whom the prostate cancer diagnosis was their first and only cancer diagnosis; men diagnosed at autopsy or on their death certificate were excluded. All eligible men were at least 65 years old with one full year of Medicare claims before their diagnosis and continuously enrolled in a Medicare FFS plan from one year pre-diagnosis to at least one year post-initial treatment. A full year of pre-diagnosis claims was required to capture pre-diagnosis comorbidities. No men with end-stage renal disease as the reason for Medicare entitlement were included, nor were those men with multiple primary cancer sites or metastatic disease upon diagnosis. The sample was further refined by focusing on men who were diagnosed with American Joint Committee on Cancer pathologic stage pT2-pT3N0M0 disease and received radical prostatectomy within 180 days of diagnosis. Men who received adjuvant radiation therapy were included where adjuvant radiation therapy was defined as external beam radiation therapy initiated within 180 days of surgery.[22] Men who received any type of neoadjuvant therapy or secondary treatment in the form of salvage radiation therapy (radiation therapy initiated more than 180 days after surgery), hormone therapy, or chemotherapy in the first year following surgery were excluded as these therapies may indicate that radical prostatectomy was not fully effective in achieving disease control. Men who received any type of secondary treatment more than one year past surgery were included in the sample until initiation of secondary therapy. Men who received adjuvant radiation therapy are included because in these men, radiation therapy is considered to be part of the initial curative treatment rather than a response to disease recurrence.

The final sample consisted of 10,761 men. The unit of observation was the person-period (where a period was 1 year or 6 months), resulting in a total of 47,042 observations for the 1 year model and 102,464 observations for the 6 month model. Partial periods of data were not included.

Figure 4. Sample Counts for Included and Excluded Observations, Aim 1



Note: SEER: Surveillance, Epidemiology and End Results; HMO: Health maintenance organization; ESRD: End stage renal disease; FFS: Fee-for-service

4.2.3. Study Outcome Measure

The primary measure of PSA surveillance testing was a binary variable indicating whether a patient received at least one PSA test during a given year following initial treatment. The surveillance period began 60 days after prostatectomy or the final radiation therapy treatment for men receiving adjuvant radiation therapy and continued to death (using SEER date of death), initiation of secondary therapy (salvage radiation therapy, hormonal therapy, or chemotherapy), a switch from Medicare FFS to HMO, or the end of available claims data (December 31, 2009). Initiation of secondary therapy is generally a response to disease recurrence and thus marks the end of the surveillance period following initial therapy. Men who received salvage radiation therapy more than one year past surgery were included in the sample until initiation of radiation therapy, whereas men who received salvage radiation therapy within one year of surgery were not included.

PSA surveillance tests were identified in Medicare claims by Healthcare Common Procedure Coding System (HCPCS) codes (84152, 84153, 84154, and G0103), and initial and secondary therapies were identified using SEER treatment variables and Medicare claims (Table 8). As strict adherence to surveillance guidelines would require PSA testing every 6 months, a measure of testing receipt was defined using a binary variable indicating whether a patient received at least one test in a given 6-month interval. The sensitivity of results to the measurement of guideline adherence also was examined by the use of a 9-month surveillance interval in addition to the 1-year and 6-month time intervals.

Table 8. Billing Codes Used to Identify Relevant Procedures in Medicare Claims

	ICD-9	CPT/HCPCS
PSA testing		84152-84154, G0103
Surgery	60.4, 60.5, 60.6x	55810, 55812, 55815, 55840, 55842, 55845, 00865, 55866
External beam radiation therapy*	92.24, 92.26	77301, 77305, 77310, 77315, 77321, 77371-77373, 77380, 77381, 77401, 77403-77409, 77411-77414, 77416, 77418, 77422, 77423, 77520, 77522, 77523, 77525, 77526, 0073T, G0178
Brachytherapy and other radiation therapy	92.20, 92.21, 92.22, 92.25, 92.23, 92.27, 92.28, 92.29	55859, 55860, 55862, 55865, 55875, 76873, 77470, 77750-77799, 79005-79999, C1164, C1174, C1325, C1350, C1700, C1701, C1702, C1715-C1720, C1728, C1790-C1806, C2638, C2639, C2640, C2641, G0256, G0261, Q3001
Hormone therapy	62.3, 62.4x	54520, 54522, 54530, 54535, 54690, J1050, J1051, J1950, J3315, S0175, J9000-J9999
Chemotherapy	99.25, V58.1x, V66.2, V67.2	96400-96549, Q0083-Q0085

*These codes capture both salvage and adjuvant radiation therapy; the distinction between the two is made by examining treatment timing relative to radical prostatectomy.

Note: ICD-9: International Classification of Diseases, 9th Revision; CPT: Current Procedural Terminology; HCPCS: Healthcare Common Procedure Coding System; PSA: Prostate-specific antigen

4.2.4. Key Independent and Control Variables

Key independent variables were time elapsed since completion of initial treatment and patient race/ethnicity. Time elapsed was measured as an indicator of whether the observation captured the first, second, third, fourth, fifth, or sixth or later year. The sixth year and beyond were combined to reflect the change in surveillance

guidelines at five years post-treatment. The SEER version of race/ethnicity was used to measure patient race/ethnicity. Medicare claims also report race/ethnicity, but it is believed that the SEER data are superior, due in part to SEER's use of a Spanish-surname algorithm.[131] Race/ethnicity was coded as non-Hispanic white, non-Hispanic black, Hispanic, and other/unknown. Details of how collapsed categories were created, along with potential values and ranges of all control variables can be found in Table 9.

Table 9. Control Variables, Values, and Sources, continued on next page

Variable	Type	Potential Values/Range	Source
Individual-level (10,359 individuals)			
Race/ethnicity	Categorical	Non-Hispanic White (Caucasian not otherwise specified), non-Hispanic Black (Black), Hispanic (Caucasian, Spanish origin or surname), Other/Unknown (American Indian/Alaska Native, Chinese, Japanese, Filipino, Hawaiian, Other Asian or Pac. Islander, Unknown, Other unspecified)	PEDSF
Age at diagnosis	Continuous*	65 - 94	PEDSF
Marital status	Binary	Married, not married (single, separated, divorced, widowed, unknown)	PEDSF
Co-morbid conditions, measured by the NCI Combined co-morbidity index	Continuous*	0 - 2.6	Claims
State buy-in at diagnosis	Binary	Yes, No	PEDSF
Pathologic tumor stage	Binary	pT2, pT3	PEDSF
Tumor histology	Binary	Well/moderately (combined Gleason score of 7 or less) or poorly differentiated (combined Gleason score of 8 or more)	PEDSF
Diagnosis year	Categorical	1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007	PEDSF

*Categorical approximations examined in models

Note: SD: Standard deviation; PEDSF: SEER Patient Entitlement and Diagnosis Summary File; SEER: Surveillance, Epidemiology, and End Results; HMO: Health maintenance organization; RTI: Research Triangle Institute; NCI: National Cancer Institute; ERS: Economic Research Service; USDA: United States Department of Agriculture; NRCRD, PSU: Northeast Regional Center for Rural Development, Penn State University

Table 9. Control Variables, Values, and Sources, continued from previous page

Variable	Type	Potential Values/Range	Source
County-level (683 counties)			
Racial isolation index	Continuous	Varies by race: Non-Hispanic White: 0.16 - 1.00 (mean 0.83, SD 0.16) Non-Hispanic Black: 0 - 0.85 (mean 0.15, SD 0.19) Hispanic: 0 - 0.87 (mean 0.13, SD 0.17) Pacific Islander: 0 - 0.17 (mean 0.004 SD 0.012) American Indian/Alaska Native: 0 - 0.84 (mean 0.03, SD 0.10) Other Asian: 0 - 0.54 (mean 0.03, SD 0.06)	U.S. Census
Persistent poverty indicator	Binary	Yes, No (mean 0.12, SD 0.33)	ERS, USDA
Population density (people per square mile)	Continuous	0.27 - 71,190 (mean 574, SD 3,248)	U.S. Census
Social capital index	Continuous	-2.60 - 4.50 (mean -0.36, SD 1.27)	NRCRD, PSU
Medicare HMO Penetration	Continuous	0 - 0.53 (mean 0.07 SD 0.11)	RTI Spatial Database

*Categorical approximations examined in models

Note: SD: Standard deviation; PEDSF: SEER Patient Entitlement and Diagnosis Summary File; SEER: Surveillance, Epidemiology, and End Results; HMO: Health maintenance organization; RTI: Research Triangle Institute; NCI: National Cancer Institute; ERS: Economic Research Service; USDA: United States Department of Agriculture; NRCRD, PSU: Northeast Regional Center for Rural Development, Penn State University

Individual-level measures of age, marital status, tumor characteristics, co-morbidity, and Medicare state buy-in at diagnosis were used to control for the likelihood that an individual would receive follow-up surveillance as part of post-treatment care. Tumor characteristics included an indicator of pathologic tumor stage (pT2 or pT3, where pT3 tumors are characterized by extraprostatic extension), and tumor histology, which was captured by a binary variable indicating whether the combined Gleason score of the tumor was less than or equal to 7 or greater than 7. Comorbidities at diagnosis were measured using the prostate cancer-specific condition weights of the National Cancer Institute (NCI) Combined Comorbidity Index, which was developed specifically

for use with SEER-Medicare data.[132] Medicare state buy-in at diagnosis was used to help control for income, healthcare access, and individual characteristics not otherwise captured. Although this indicator has previously been used to identify low-income individuals who are dually-eligible for Medicare and Medicaid, a recent study cast doubt on the adequacy of the buy-in indicator to appropriately identify all dually-eligible individuals.[133]

County-level measures of population density,[120] persistent poverty,[134] racial isolation,[135] social capital,[136] and Medicare HMO penetration[120] were included in the models to control for access to care, community-level social support and local practice patterns. These county variables were specific to the last known county in which each individual received a PSA test, based on address from the associated Medicare claim. Using the claim address rather than the SEER registry address (recorded at the time of first cancer diagnosis) may be important as patients may move from the area in which they were diagnosed. A continuous measure of annual population density (1,000 individuals per square mile) was used to control for geographic isolation and as a potential measure of access to care. An additional control for access to care was an indicator of persistent poverty for the year 2004, which indicates that at least 20% of the county population had a household income below the poverty level in the last 4 decennial U.S. censuses.[134] A race-specific measure of racial isolation/segregation was included to capture the social support networks available in each individual's community.[135] This measure is based on 2000 U.S. Census data and has been shown to influence receipt of screening mammography in the Medicare population.[137] This index measures the extent to which racial minority members are exposed to (live in counties with) members of their own race rather than non-minority members. Each index value is race- and county-specific, so each individual in the sample has an index value that

corresponds to the likelihood they will come into contact with members of their own race within their county of residence.

A measure of community social capital that may influence an individual's ability to seek and obtain medical care was also included. This 2005 county-level measure is a composite index based on the number of civic and non-profit organizations in the county, voter turn-out, and Census return rates.[136] Finally, a county-level measure of the percent of Medicare beneficiaries participating in an HMO plan was used to control for variations in practice patterns that may be attributable to a managed care spillover effect.[138] This phenomenon occurs when managed care penetrates a local health care market and affects the diffusion of technologies and/or local practice patterns. These effects have been shown to exist in colorectal cancer screening practices among FFS Medicare enrollees.[161,162] This measure was available for the years 2001-2005; the 2001 value was assigned to observations from 1998-2001 and the 2005 value was assigned to observations from 2005-2009.

4.2.5. Statistical Analysis

To examine the data, I calculated summary statistics and performed bivariate statistical tests, specifically t-tests for continuous variables and chi-square tests for binary and categorical variables.[154] I estimated logistic regression models, using a generalized estimating equations (GEE)-based approach to account for the correlation between the person-year observations, to evaluate the influence of covariates on receiving a PSA test in a given time interval. Separate models were used to estimate the likelihood of receiving one test over 1-year, 6-month, and 9-month time intervals. All models were estimated using a limited set of control variables consisting of year or period indicators to measure time elapsed since treatment and a full set of control variables including individual, tumor, and county-level factors. The appropriateness of model specification and error term correlation structure were evaluated using Wald test

statistics[154] and the quasi-likelihood under the independence model information criterion (QIC).[155] Individual coefficients are reported in terms of odds ratios (ORs), and statistical significance was determined by examining the estimated z-statistics, using an alpha of .05.[154] All models were estimated using robust standard errors, which essentially clusters on the individual. Stata, version 10 (StataCorp, College Station, TX), which was used for the data analysis, does not allow for clustering on additional panel variables in the GEE framework, so no adjustment was made for SEER registry or county of residence. Thus the county contextual variables may exhibit redundancy among individuals within the same county, leading to potential overstated statistical significance for the associated coefficients. Results related to county- and registry-level variables should therefore be interpreted cautiously. However, clustering at the registry level may be unadvised as the small number of clusters and unbalanced cluster size could increase rather than decrease bias in the standard error estimates.[163] Additionally, individual-level clustering was considered superior to county-level clustering as this analysis placed primary importance on the interpretation of individual-level coefficients.

I compiled the data both in SAS, version 9.1 (SAS, Cary, NC) and Stata, version 10 (StataCorp, College Station, TX). I performed all data analysis in Stata. This research was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill.

4.3. Results

4.3.1. Descriptive Statistics

The average age at diagnosis for men in the sample was 69.5 years (standard deviation [SD] = 3.1), and follow-up times ranged from one to 11 years. Average follow-up time overall was 4.5 years (SD = 2.7). The sample was primarily non-Hispanic White (83.3%), with an additional 5.8% non-Hispanic Black, 6.1% Hispanic, and 4.8% of other/unknown race/ethnicity, of whom 21% were Japanese, 39% were other Asian or Pacific Islander,

and 15% were of unknown race/ethnicity. Eighty-two percent of the men were diagnosed with pT2 disease (as opposed to pT3), and most men (84.5%) had well/moderately differentiated tumors, defined by a combined Gleason score of 7 or less.

Table 10. Sample Characteristics for Men Receiving at Least One PSA Test per Year versus Men with at Least One Year with no PSA Test, over First 5 Years of Surveillance, continued on next page

	Overall % or mean (SD)	One or more years with no test	At least one annual test	p-value†
Number of observations	10,761	2,606	8,155	
Age at diagnosis	69.5 (3.1)	69.6 (3.2)	69.5 (3.0)	.0285
Age by category (%)				.0592
65-69	57.3	55.3	58.0	
70-74	35.6	37.0	35.1	
75 +	7.1	7.7	7.0	
Married at diagnosis (%)	82.0	79.5	82.8	.0002
State buy-in at diagnosis (%)	6.4	8.7	5.7	< .0001
Tumor Histology (%)				.0029
Well/Moderately differentiated	84.5	82.6	85.1	
Poorly differentiated	15.5	17.4	14.9	
Pathologic stage T2 (%)	82.3	85.4	81.3	< .0001
NCI Comorbidity Index at diagnosis	0.10 (0.25)	0.11 (0.26)	0.10 (0.25)	.3199
NCI Comorbidity Index by category (%)				.4855
0	78.3	77.8	78.5	
> 0	21.7	22.2	21.5	
Race (%)				.0065
Non-Hispanic White	83.3	81.6	83.8	
Non-Hispanic Black	5.8	6.5	5.6	
Hispanic	6.1	7.3	5.7	
Other/Unknown	4.8	4.6	4.9	

† p-values obtained using t-tests and chi-square tests and apply to differences in percentages or means across columns 3 and 4.

Note: PSA: Prostate-specific antigen; HMO: Health maintenance organization; NCI: National Cancer Institute; SD: Standard deviation

Table 10. Sample Characteristics for Men Receiving at Least One PSA Test per Year versus Men with at Least One Year with no PSA Test, over First 5 Years of Surveillance, continued from previous page

	Overall % or mean (SD)	One or more years with no test	At least one annual test	p-value†
Year of diagnosis (%)				< .0001
1998	4.3	6.3	3.7	
1999	4.5	6.5	3.9	
2000	7.8	9.9	7.1	
2001	9.5	13.1	8.4	
2002	10.5	14.2	9.3	
2003	10.7	14.1	9.7	
2004	12.4	12.9	12.2	
2005	11.8	9.7	12.5	
2006	12.8	7.9	14.4	
2007	15.6	5.4	18.9	
Years in sample	4.5 (2.7)	5.7 (2.4)	4.1 (2.6)	< .0001
County-level persistent poverty (%)	3.3	3.7	3.2	.2445
Race-specific isolation index	0.71 (0.21)	0.71 (0.21)	0.71 (0.21)	.9403
County-level social capital index	-0.68 (1.03)	-0.63 (1.06)	-0.70 (1.01)	.0023
County population density (1000s per square mile)	1.28 (2.03)	1.30 (2.25)	1.28 (1.95)	.6653
County-level HMO penetration	16.3 (15.1)	16.1 (15.3)	16.4 (15.0)	.4571

† p-values obtained using t-tests and chi-square tests and apply to differences in percentages or means across columns 3 and 4.

Note: PSA: Prostate-specific antigen; HMO: Health maintenance organization; NCI: National Cancer Institute; SD: Standard deviation

Overall, men received an average of 2.0 (SD = 1.0) PSA tests per year after treatment, but nearly 25% went at least one year without a test during the first 5 years after treatment. Table 10 presents characteristics of the study sample stratified by men who received at least one test each year for the first 5 years after treatment and those men who did not. Non-Hispanic White men, men diagnosed and treated at younger ages, married men, and men diagnosed with stage pT3 disease were more likely to receive at least one annual test during the first 5 years after treatment than other races;

men treated at older ages; single, widowed, or divorced men; and men with stage pT2 disease, respectively. The t-test results revealed that social capital was the only county-level variable differing significantly across men who received at least one annual test versus those who did not.

Figures 5 and 6 present the proportion of the sample receiving annual PSA tests by year of diagnosis and time elapsed since treatment. Regardless of year of diagnosis, almost all men receive at least one PSA test in the first year after treatment, ranging from 94% for men diagnosed in 1999 to 97% for men diagnosed in 2005 ($p = .0026$) (Figure 5). Over time post-treatment, the percentage of men receiving at least one test falls significantly ($p < 0.0001$ for the percentage of men receiving a test in year 1 versus the percentage of men receiving a test in year 5). By 5 years after treatment, there is no significant difference in test receipt by year of diagnosis; the percentage ranges from 80% for men diagnosed in 1999 to 81% for men diagnosed in 2003. The drop in annual receipt of testing is even greater when using a strict guideline-concordant PSA surveillance definition of receipt of at one test in each 6-month period (Figure 6). At least 85% of men receive one PSA test in the first 6 months after treatment, regardless of year of diagnosis, but this falls to approximately 55% of men 5 years (10 6-month periods) after treatment.

Figure 5. Percentage of Sample Receiving at Least One Surveillance Prostate-specific Antigen Test, for Selected Years of Diagnosis

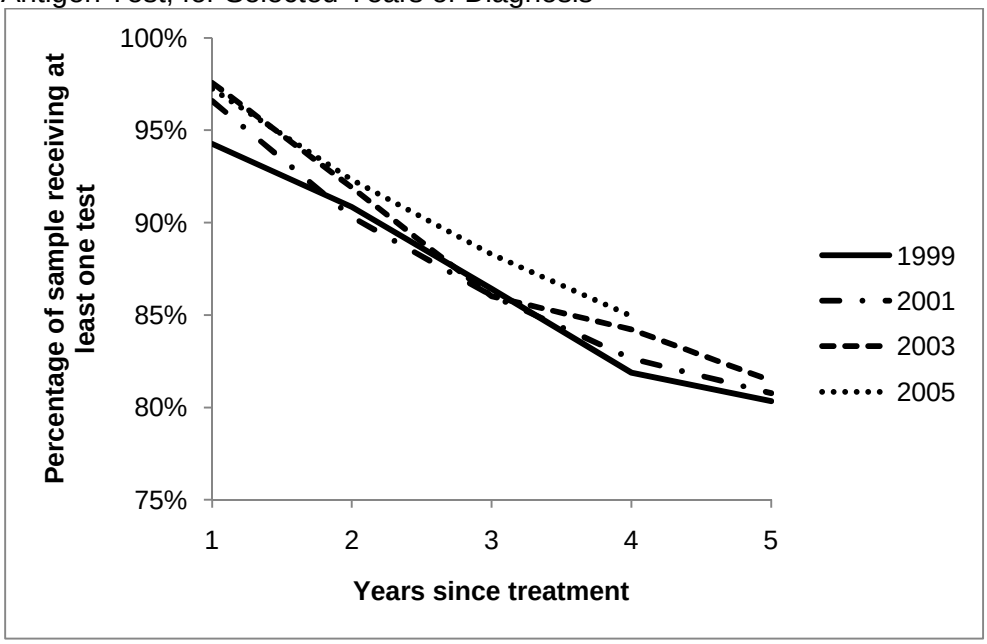
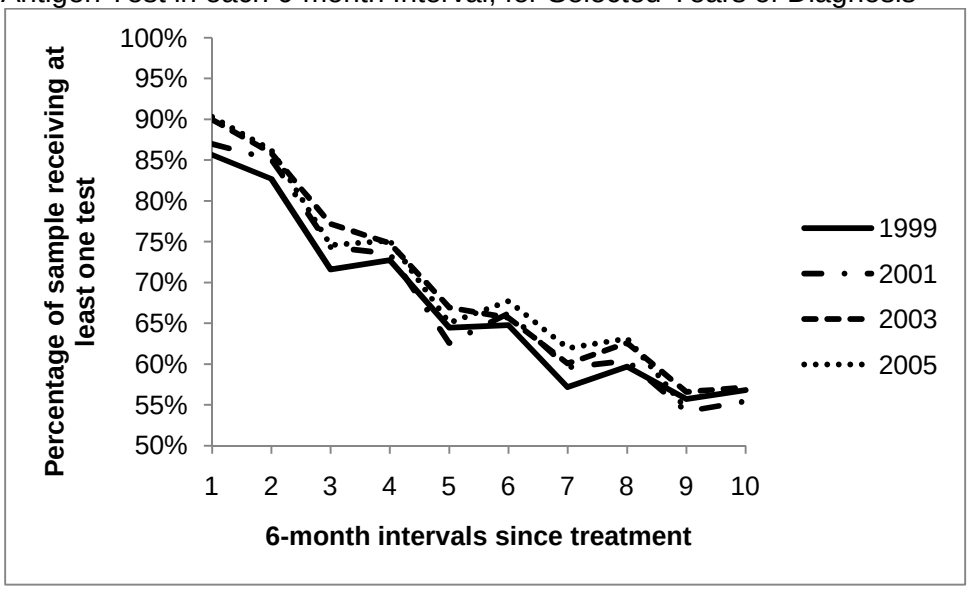


Figure 6. Percentage of Sample Receiving at Least One Surveillance Prostate-specific Antigen Test in each 6-month Interval, for Selected Years of Diagnosis



By race, non-Hispanic Whites and those of other/unknown race have consistently higher rates of annual test receipt in the years following treatment than non-Hispanic Blacks and Hispanics (Figure 7), although the minority sample sizes are relatively small.

All 4 racial groups (non-Hispanic White, non-Hispanic Black, Hispanic, other/unknown) begin with high rates of test receipt. The largest gap in the first year following treatment is observed between non-Hispanic Whites (96.7%) and Hispanics (94.7%) ($p = .0119$). The gap between races widens as time from treatment increases. By 5 years post-treatment, the test receipt rate among non-Hispanic Whites is highest, at 82.3% and is 6.5 percentage points higher than the lowest testing rate, which is observed in Hispanics (75.8%) ($p = .0039$). A large difference was also observed between non-Hispanic Whites and non-Hispanic Blacks at 5 years post-treatment (82.3% versus 76.5%) ($p = .0196$).

Figure 7. Percentage of Sample Receiving at Least One Surveillance Prostate-specific Antigen Test, by Race/ethnicity

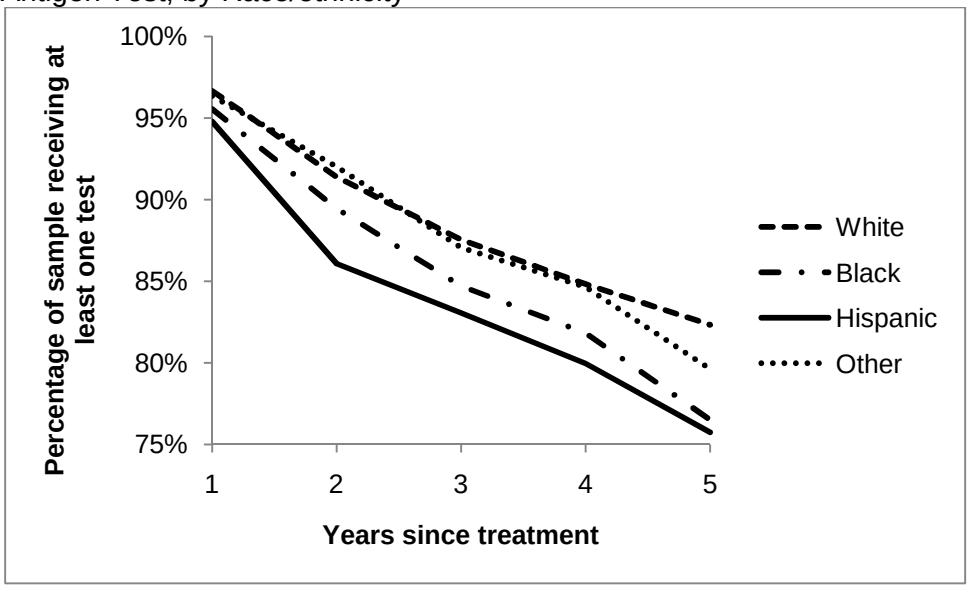
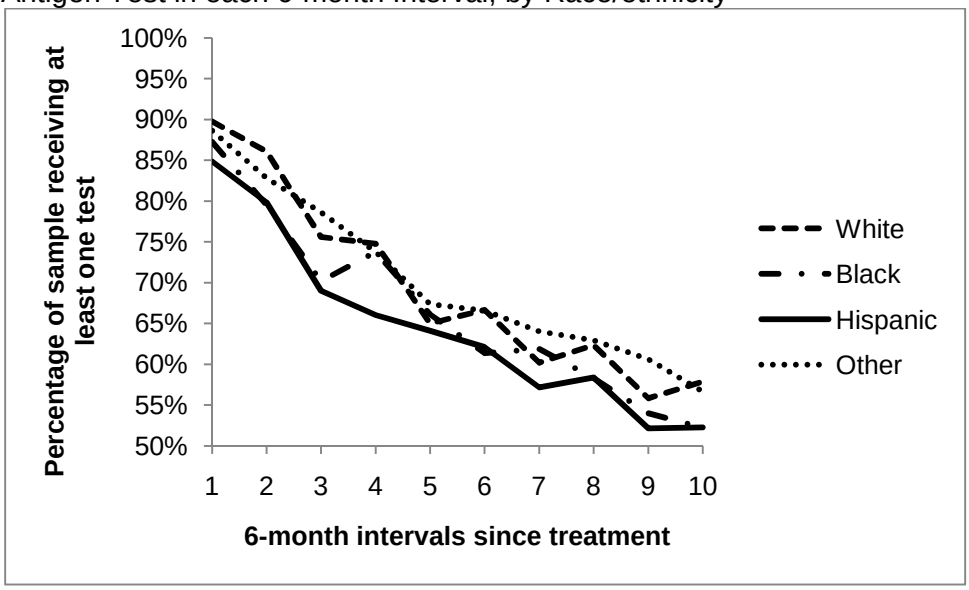


Figure 8. . Percentage of Sample Receiving at Least One Surveillance Prostate-specific Antigen Test in each 6-month Interval, by Race/ethnicity



Hispanics also have consistently lower rates of surveillance PSA testing than other racial groups when defining PSA test receipt as at least one test in a 6-month interval (Figure 8). Unlike the results found when considering a 1-year testing interval, the difference between the most frequently and least frequently tested groups does not appreciably increase over time. In the first 6-month interval following treatment, 89.7% of non-Hispanic Whites receive a PSA test, compared to 84.8% of Hispanics (a difference of 4.9 percentage points) ($p = .0001$). By the 10^{th} 6-month interval, the difference between the two racial groups was 5.6 percentage points ($p = .0565$). Although there is a downward trend, testing rates are not strictly decreasing over time, that is, the rate in a given interval is not necessarily less than the rate in the previous interval. This is particularly true for non-Hispanic Whites and non-Hispanic Blacks.

4.3.2. Multivariate Logistic Regression Analysis

To better understand the observed decrease in testing each interval past treatment, I estimated logistic models to examine the effect of time elapsed since treatment on test receipt. These models were run with (fully-adjusted) and without

(partially-adjusted) other control variables. Table 11 presents these results for the receipt of at least one test in a 1-year interval. In both models, the effect of time elapsed since treatment is large and significant. Without controlling for individual or county-level characteristics, men 2 years past treatment have lower odds of receiving at least one test than men one year past treatment (OR = 0.37, 95% confidence interval [CI] = 0.33-0.42). The odds are lower for men 3 years past treatment (OR = 0.25, 95% CI = 0.22-0.28), and lower still for men 4 years past treatment (OR = 0.19, 95% CI = 0.17-0.22). The largest decrease in odds from one year to the next (for estimated coefficients) is seen between years 2 and 3. All estimated odds ratios are statistically significant and statistically different from one another. Similar results were observed when restricting the sample to men with at least 5 years of observation (results not reported).

Table 11. Logistic Regression Results for Receipt of One PSA Surveillance Test During a 1-year Interval, continued on next page

	Partially-adjusted		Fully-adjusted	
	OR	95% CI	OR	95% CI
Years since treatment (1 is reference)				
2	0.37***	0.33-0.42	0.36***	0.32-0.40
3	0.25***	0.22-0.28	0.24***	0.21-0.26
4	0.19***	0.17-0.22	0.18***	0.16-0.21
5	0.16***	0.14-0.18	0.15***	0.14-0.18
6 or more	0.11***	0.10-0.12	0.10***	0.09-0.12
Age at diagnosis			0.98**	0.97-0.99
Not married at diagnosis			0.83***	0.75-0.92
State buy-in at diagnosis			0.68***	0.57-0.81
Tumor poorly differentiated			0.95	0.85-1.06
Pathologic stage T2			0.83**	0.74-0.93
NCI Comorbidity Index at Diagnosis			0.94	0.80-1.10
Race (Non-Hispanic White is reference)				
Non-Hispanic Black			0.78*	0.64-0.94
Hispanic			0.76**	0.63-0.91
Other/Unknown			0.99	0.76-1.30

* significant at 5%, ** significant at 1%, *** significant at 0.1%, robust standard errors used

Note: OR: Odds ratio; CI: Confidence interval; PSA: Prostate-specific antigen; HMO: Health maintenance organization; NCI: National Cancer Institute; QIC: Quasi-likelihood under the independence model information criterion

Table 11. Logistic Regression Results for Receipt of One PSA Surveillance Test During a 1-year Interval, continued from previous page

	Partially-adjusted		Fully-adjusted	
	OR	95% CI	OR	95% CI
Year of diagnosis (1998 is reference)				
1999			0.83	0.68-1.00
2000			0.95	0.79-1.15
2001			0.93	0.78-1.12
2002			0.99	0.83-1.18
2003			1.02	0.85-1.22
2004			1.09	0.89-1.32
2005			1.11	0.90-1.37
2006			0.91	0.73-1.14
2007			0.87	0.68-1.10
County-level persistent poverty			0.82	0.65-1.04
Race-specific isolation index			0.74	0.53-1.01
County-level social capital index			0.98	0.94-1.02
County population density			1.01	0.99-1.03
County-level HMO penetration			1.18	0.85 - 1.64
Person-year observations	48,426		47,033	
Men	10,761		10,496	
QIC	35,927		34,713	

* significant at 5%, ** significant at 1%, *** significant at 0.1%, robust standard errors used

Note: OR: Odds ratio; CI: Confidence interval; PSA: Prostate-specific antigen; HMO: Health maintenance organization; NCI: National Cancer Institute; QIC: Quasi-likelihood under the independence model information criterion

The results from the fully-adjusted multivariate regression model mirror those results found in the bivariate analyses. Men who were not married, had state buy-in at diagnosis, and who were diagnosed at older ages had lower odds of receiving at least one PSA test in a given year. Men with pT2 tumors had 0.83 lower odds (95% CI = 0.74-0.93) of receiving at least one PSA test than men with pT3 tumors. Tumor differentiation and comorbidities at diagnosis were not found to be significant predictors of the likelihood of receiving at least one test in a given year. None of the coefficients associated with county-level factors were significant, nor was the year of diagnosis. The

inclusion of individual and county characteristics only slightly changed the estimated odds ratios associated with years elapsed since treatment (Table 11). All odds ratios for years elapsed since treatment remain statistically significant individually, are statistically significantly different from one another, and decrease with time elapsed since treatment.

The odds ratios estimated for racial characteristics reflect the results shown in Figures 7 and 8. Men of other/unknown race had odds of test receipt equivalent to non-Hispanic Whites, whereas non-Hispanic Blacks and Hispanics had significantly lower odds than non-Hispanic Whites (OR = 0.78 with 95% CI = 0.64-0.94 for non-Hispanic Black and OR = 0.76 with 95% CI = 0.63-0.91 for Hispanic, with non-Hispanic White as the referent). The odds for non-Hispanic Black and Hispanic were not significantly different from one another.

Most of the factors that affect the likelihood an individual will receive at least one test in a year also affect the likelihood that he will receive at least one test in a 6-month interval, with the exception of age at diagnosis (Table 12). In contrast to the results for the 1-year interval, 4 of the 5 county-level factors affect the odds of receiving at least one test within a 6-month interval. Higher Medicare HMO penetration and population density are associated with higher odds of receiving at least one test (OR = 1.420 with 95% CI = 1.17-1.72 and OR = 1.01 with 95% CI = 1.00-1.03, respectively). Higher levels of the county-level social capital index and the race-specific county-level isolation index are associated with lower odds of receiving one test (OR = 0.97 with 95% CI = 0.94-0.99 for the social capital index and OR = 0.74 with 95% CI = 0.61-0.89 for the isolation index). With the exception of 2004, year of diagnosis has no influence on the odds a man will receive at least one test in a 6-month interval.

Table 12. Logistic Regression Results for Receipt of One PSA Surveillance Test During a 6-month Interval, continued on next page

	Partially-adjusted		Fully-adjusted	
	OR	95% CI	OR	95% CI
6-month periods since treatment (1 is reference)				
2	0.69***	0.64-0.74	0.68***	0.63-0.74
3	0.36***	0.34-0.39	0.36***	0.34-0.39
4	0.35***	0.32-0.37	0.34***	0.32-0.37
5	0.22***	0.21-0.24	0.22***	0.21-0.24
6	0.23***	0.22-0.25	0.23***	0.22-0.25
7	0.18***	0.17-0.20	0.18***	0.17-0.20
8	0.20***	0.18-0.21	0.20***	0.18-0.21
9	0.15***	0.14-0.16	0.15***	0.14-0.17
10	0.16***	0.15-0.17	0.16***	0.15-0.18
11 or more	0.11***	0.10-0.11	0.11***	0.10-0.12
Age at diagnosis			0.99	0.99-1.00
Not married at diagnosis			0.89***	0.84-0.95
State buy-in at diagnosis			0.75***	0.67-0.84
Tumor poorly differentiated			0.99	0.93-1.06
Pathologic stage T2			0.83***	0.78-0.89
NCI Comorbidity Index at Diagnosis			1.01	0.92-1.12
Race (Non-Hispanic White is reference)				
Non-Hispanic Black			0.86*	0.77-0.97
Hispanic			0.80***	0.71-0.89
Other/Unknown			0.92	0.79-1.08
Year of diagnosis (1998 is reference)				
1999			0.93	0.82-1.05
2000			1.01	0.90-1.13
2001			0.98	0.88-1.10
2002			1.03	0.92-1.15
2003			1.12	1.00-1.25
2004			1.12*	1.00-1.26
2005			1.11	0.98-1.24
2006			1.11	0.99-1.26
2007			1.12	0.99-1.28

* significant at 5%, ** significant at 1%, *** significant at 0.1%, robust standard errors used

Note: OR: Odds ratio; CI: Confidence interval; PSA: Prostate-specific antigen; HMO: Health maintenance organization; NCI: National Cancer Institute; QIC: Quasi-likelihood under the independence model information criterion

Table 12. Logistic Regression Results for Receipt of One PSA Surveillance Test During a 6-month Interval, continued from previous page

	Partially-adjusted		Fully-adjusted	
	OR	95% CI	OR	95% CI
County-level persistent poverty			1.00	0.86-1.15
Race-specific isolation index			0.74**	0.61-0.89
County-level social capital index			0.97*	0.94-0.99
County population density			1.01*	1.00-1.03
County-level HMO penetration			1.42***	1.17-1.72
Person-year observations	102,464		99,736	
Men	10,636		10,425	
QIC	121,293		117,346	

* significant at 5%, ** significant at 1%, *** significant at 0.1%, robust standard errors used

Note: OR: Odds ratio; CI: Confidence interval; PSA: Prostate-specific antigen; HMO: Health maintenance organization; NCI: National Cancer Institute; QIC: Quasi-likelihood under the independence model information criterion

The odds ratios for receipt of surveillance PSA associated with 6-month intervals beyond treatment are nearly identical in the fully-adjusted model and the partially-adjusted model (Table 12). Generally, each 6-month period elapsed since treatment is associated with lower odds of receiving a test, but the odds are not strictly decreasing after five 6-month periods (2 ½ years) past treatment. After the fifth interval, the odds increase and decrease with respect to the previous period, reflecting the percentages graphed in Figures 6 and 8. With the exception of the odds ratios for period 3 compared to period 4, period 5 compared to period 6, and period 9 compared to period 10, all period-related odds ratios are significantly different from the next 6-month period.

All racial categories are associated with lower odds of receiving a test in a 6-month interval compared to non-Hispanic Whites, although the difference is only significant for non-Hispanic Blacks (OR = 0.86 with 95% CI = 0.77-0.97) and Hispanics (OR = 0.80 with 95% CI = 0.71-0.89). The difference in odds ratios between non-Hispanic Black and Hispanic is larger in magnitude than the corresponding difference

from the results of the model examining receipt of at least one test in a year, but the odds ratios are not statistically different from one another (p = .2907).

To further test the sensitivity of the results to the time interval, additional models were estimated using a 9-month interval. The estimated coefficients from the 9-month partially- and fully-adjusted models are similar to those for the 1-year interval models and are not presented.

4.4. Discussion

Overall, most men were found to be receiving post-treatment surveillance PSA tests in line with guideline recommendations. With an average of two tests per year during the entire observation period, men met the recommended surveillance schedule of a PSA test every 6 months. During the study period, the NCCN Guidelines changed the recommended surveillance interval from every 6 months to every 6 to 12 months for the first five years after treatment. By this revised schedule, approximately 80% of men received surveillance in accordance with guidelines in the fifth year past treatment, regardless of year of diagnosis. By a strict adherence definition of a test every 6 months (which was recommended under the NCCN Guidelines from 1998 to 2007), approximately 55% of men overall received the recommended surveillance in the fifth year after treatment.

By far, the most important factor influencing whether a man receives a PSA test is time elapsed since treatment. This is supported not only by the comparison of results from the partially-adjusted and fully-adjusted models, but by the relative size of the odds ratios associated with the time period variables compared with the estimated odds ratios associated with other control variables. Test receipt drops significantly each year for the first 5 years after treatment. This is troubling given that most prostate cancer recurrences generally occur in the first 5 years after local therapy,[4] and 25%-30% of these men could be expected to experience PSA recurrence.[1] The majority of men at 5

years from treatment do, however, receive at least one test during the year, which suggests that these men are still receiving some form of follow-up care, although it is unknown whether this test is administered by a general practitioner as part of usual care or by a urologist (or other health practitioner) as part of a cancer survivorship plan.

The observed rate of surveillance test receipt is high compared to a study of surveillance mammography following breast cancer treatment which found that only 19% of the study sample was in compliance with surveillance recommendations at 3 years following treatment.[56] A study of colorectal cancer survivors reported that more than half of the sample did not receive a guideline-recommended surveillance colonoscopy within 14 months of treatment.[53] Despite these comparatively low surveillance rates, care should be taken not to overstate any differences in post-treatment surveillance between prostate cancer survivors and breast and colorectal cancer survivors as PSA testing is less invasive and less costly than either mammography or colonoscopy.

Although time elapsed since treatment dominates the results, there are other interesting findings. Non-Hispanic Blacks and Hispanics have lower odds of receiving tests than non-Hispanic Whites and men of other/unknown race for both the 1-year and 6-month intervals. There was no significant difference in surveillance intensity between non-Hispanic Blacks and Hispanics. This finding of a racial disparity between non-Hispanic Whites and other groups is in accord with previously reported racial differences in prostate cancer treatment and mortality,[68,69] and the difference in test receipt between non-Hispanic Blacks and non-Hispanic Whites is in line with the results reported in the only other study to focus on post-treatment PSA receipt.[70] Although the racial disparity results in no way suggest that differences in surveillance lead to differences in mortality, they do suggest that the difference in surveillance by race may be clinically significant in addition to statistically significant. Given that previous research has demonstrated a racial disparity in prostate cancer overall survival among Medicare surgery patients

when controlling for individual and tumor characteristics,[159] the link between surveillance and outcomes in minority prostate cancer patients is a topic worthy of future investigation.

The year of diagnosis does not appear to affect the likelihood of receiving a PSA test in either the 1-year or 6-month interval. Graphical results suggested that there may have been higher receipt of surveillance testing in men diagnosed in later years, but the regression results did not support this pattern.

Many of the county-level variables had an effect on the odds of receiving a test in a 6-month interval but not in a 1-year interval. The four significant county-level variables in the 6-month model represent two constructs that may affect care utilization. Medicare HMO penetration and population density are highly correlated with urbanicity, which implies better access to care. Social capital and isolation are correlated with social support systems. The high rates of surveillance over the 1-year interval could indicate that an annual surveillance test is a low threshold of care that is easily met. Getting tested every 6 months may require more resources and motivation, thus access to care and social support may play a larger role in the likelihood an individual will receive a PSA test in a 6-month period.

Particularly, higher isolation indices were associated with lower odds of receipt of a test in a 6-month interval. That is, individuals living in areas where they are more likely to come into contact with individuals of their own race or ethnicity (e.g. more racially segregated/isolated) have lower odds of test receipt. This index has previously been found to have differential effects by race and geographic region on the receipt of mammography,[137] and future investigation is warranted to determine whether the same patterns hold for PSA testing and other dimensions of prostate cancer care.

The odds ratios from the 6-month model suggest that access to care is more important than social support in positively affecting PSA test utilization. It is possible

however, that instead of measuring social support, the racial isolation index is capturing geographic disparities in care related to race. The effects of race and geographic area are difficult to tease apart since individuals of different races and ethnicities are not randomly distributed across geographic areas. For example, if all Hispanic men in the sample live in areas where access to Spanish-speaking providers is limited, low surveillance rates in this population may be inappropriately attributed to ethnicity rather than access to care. The relationship between race/ethnicity and place could be explored in future work by modeling the effect of the isolation index and other community-level factors on PSA testing in each state individually. The existing literature on disparities in prostate cancer treatment and outcomes has not focused on the role communities may play in access to care and social support, and future work also could examine the influence of community characteristics on outcomes other than surveillance.

This study is limited by the use of claims data to identify PSA testing, as claims provide no information on test motivation. That is, there is no way to distinguish between men who are receiving multiple tests to follow-up on previous test results and men who are receiving multiple tests due to lack of communication across providers. Furthermore, the results of the PSA tests are not available in these data, which limits the ability to draw conclusions regarding the frequency of abnormal (in this context, detectable) PSA results and any actions (i.e., initiation of salvage treatment) that might be indicated on the basis of those results.

The limitation of the sample to men with Medicare FFS insurance means that results may not be generalizable to the entire prostate cancer population or to the entire Medicare population. Medicare HMO penetration rates had a significant effect on the odds of receiving a test in the 6-month interval model, so there is suggestion of an HMO spillover effect. Men living in counties with higher Medicare HMO penetration had higher odds of receiving a test in a 6-month interval than men who lived in areas with lower

Medicare HMO penetration rates. This suggests that HMO penetration in an area impacts local practice patterns even among individuals who are not part of a managed care plan. These spillover effects have been shown to exist in colorectal cancer screening practices although there is geographic variation in the size and direction of the effect.[161,162,164] Individual state-level models could help to clarify the role of HMO penetration in PSA surveillance test receipt.

The results of this study are also only applicable to the portion of prostate cancer patients and survivors who receive radical prostatectomy soon after diagnosis. As more than 80% of the men in SEER-Medicare with qualifying disease characteristics did not meet the surgical inclusion criteria for this study, the group of men to whom these results can be generalized is relatively small. Future research should investigate whether the same testing patterns are observed in men treated with radiation therapy or active surveillance. Additionally, findings of this study may not apply to younger men who are not covered by Medicare as these men may face a different set of competing health risks and experience different treatment patterns.[16,18] Finally, given the relatively long natural history of clinically localized prostate cancer, with a median of 8 years from the time of PSA recurrence after treatment to the development of metastatic disease,[4] future study in cohorts with long-term follow-up is needed to ascertain the relationship between post-treatment PSA surveillance, secondary treatment with salvage therapy, and metastasis-free, disease-specific and overall survival. Surveillance for early detection of recurrent cancer after treatment with curative intent is predicated on the fundamental assumption that effective salvage treatment may alter the natural history of disease progression. Evidence supporting this fundamental assumption could justify the consideration of post-treatment surveillance as a process measure for quality of cancer care.

The primary finding of this study is that most men are receiving surveillance PSA testing in line with current NCCN Guideline recommendations following radical

prostatectomy. Nevertheless, adherence rates are not perfect, and, perhaps more importantly, test receipt declines as time from treatment increases, a result that was robust across model specifications, patient groups, and testing intervals. These results suggest that one way to improve test receipt may be to focus on creating educational interventions underscoring the rationale for follow-up strategies that span many years following treatment and to highlight the significance of long-term follow-up as part of a survivorship care plan. Although there were some differences in test receipt across racial groups, individual characteristics, and tumor stage at diagnosis, the magnitude of the odds ratios associated with these factors compared to the odds ratios associated with time intervals from treatment suggest that decreasing these disparities may not be the most efficient strategy to increase overall long-term surveillance. Therefore, emphasizing the importance of disease surveillance through regular PSA testing to all patients and providers is key to high-quality long-term care as patients make the transition from cancer patient to cancer survivor.

5. VALIDATION OF ADJUVANT RADIATION THERAPY RECEIPT FOLLOWING RADICAL PROSTATECTOMY IN SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS DATA

5.1. Introduction

Recent clinical trial results have demonstrated that adjuvant radiation therapy (ART) improves recurrence-free survival in men with high-risk features in their radical prostatectomy surgical pathology.[6,7,9] As a result, the National Comprehensive Cancer Network (NCCN) revised their guidelines to suggest that ART be offered to all men with adverse pathological features or detectable prostate-specific antigen (PSA) level after prostatectomy.[22] The clinical trial results, along with the NCCN change, have sparked interest in quantifying the percentage of men for whom ART should be recommended who actually receive it.

Two recent studies using Surveillance, Epidemiology, and End Results (SEER) data to examine the receipt of ART in men with qualifying disease characteristics in the period before and after the presentation and publication of clinical trial data have found low rates of ART, but they did not confirm radiation receipt using claims data.[86,87] Although it may be several years before the effect of the ART trial results on clinical practice patterns can be fully established, an enhanced understanding of the dissemination of ART in real-world practice could potentially inform the design of future interventions targeted to populations who may not be receiving guideline-recommended care.

The Surveillance, Epidemiology, and End Results (SEER) program provides information on first course of treatment following a cancer diagnosis for people living within registry areas.[90] Historically, SEER data captured initial treatment occurring within

four months of diagnosis,[90] but beginning in 1998, SEER coding manuals instructed that all treatments included in a documented treatment plan be considered as part of the initial course of therapy, regardless of when they occur.[165] The most recent comparison of SEER primary treatment documentation and Medicare claims for radiation therapy was published in 2002 and used data from patients diagnosed with prostate cancer from 1991 to 1996.[34] In addition to changes in coding standards, since this time, there has been growing recognition that ART may offer benefits in terms of recurrence-free survival for select prostate cancer patients. These changes in documentation and treatment patterns warrant a contemporary comparison of SEER and Medicare radiation treatment variables.

A number of studies in the breast cancer literature have sought to investigate the concordance between the treatment reported in cancer registries and treatment received according to claims data.[94,96,166] Two of these studies compared registry records to Medicare claims,[94,166] whereas the third compared SEER records to self-reported treatment received.[96] For women diagnosed from June 2005 to February 2007 in Los Angeles and Detroit, SEER records failed to capture radiation therapy for 21% of women who say they received it.[96] Rates of underascertainment varied by region, chemotherapy and mastectomy receipt, stage, income, and characteristics of the diagnosis hospital. Additionally, in Los Angeles, underascertainment was associated with younger age. The authors conclude that the use of SEER data (or data from other registries) alone may result in underascertainment of radiation therapy, particularly when there is a delay or increased time between surgery and radiation therapy.[96] These findings support the motivation for the present study as the decision to deliver ART may not be made until after radical prostatectomy and surgery recovery, resulting in variations in time from surgery to radiation as well as modifications to the original treatment plan.

5.2. Methods

5.2.1. Data and Population

Data for the analysis came from the linked SEER-Medicare database. The SEER program collects population-based data on all incident cancer cases among residents of participating reporting areas. Twenty-eight percent of the U.S. population is covered by the SEER program, and the most recent SEER update contains information from 17 reporting areas on 27 cancer sites and sub-sites through 2007. The SEER registries collect information on patient demographics, cancer site, extent of disease, tumor characteristics, initial treatment, and vital status follow-up.[119] Patient demographic characteristics include age at diagnosis, race/ethnicity, marital status, and county of residence at diagnosis.

Medicare is the primary health insurance provider for 97% of the U.S. population aged 65 and older.[90] All beneficiaries receive Part A benefits, which cover inpatient hospital, skilled nursing facility, home health, and hospice care. Ninety-five percent of beneficiaries pay a monthly premium for Medicare Part B, which covers physician services, outpatient care, and durable medical equipment. Parts A and B together can take the form of a fee-for-service (FFS) or HMO plan. The Medicare Enrollment Database contains information on enrollment, entitlement, HMO membership, and demographic characteristics for each individual in the Medicare program.[90]

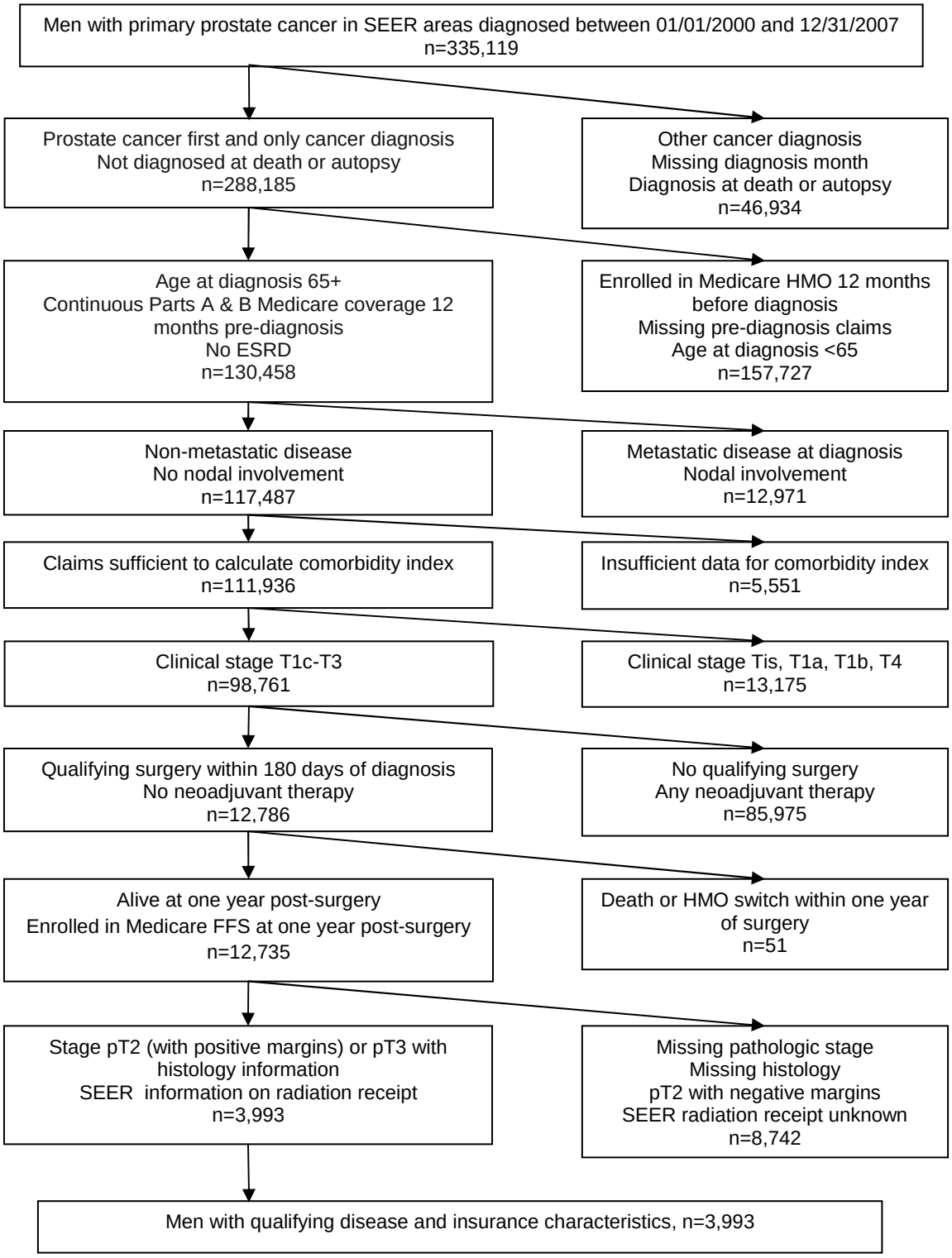
The current SEER-Medicare data linkage contains data on all cancer diagnoses and all Medicare claims for individuals participating in a Medicare FFS plan. Cancer diagnosis information is available through December 31, 2007, and Medicare claims are available through December 31, 2009.[119] The Medicare files available through the linkage include claims from hospital, outpatient, physician, home health, and hospice providers. Each file contains patient demographic characteristics, date of service, diagnostic and procedure codes, and associated charges and reimbursement.[90] Claims

are not available for Medicare participants enrolled in HMO plans. HMO penetration rates vary substantially across SEER reporting areas, with California having the highest HMO penetration at 38%.[90] The proportion of Medicare beneficiaries in SEER areas enrolled in HMOs is greater than the nationwide proportion enrolled in HMOs, but this difference has decreased over time.[90] Nationwide, the proportion of Medicare beneficiaries participating in HMO plans averaged 13% from 2001 to 2005, and 18% of Medicare beneficiaries in SEER areas participated in HMO plans over the same time period.[120]

5.2.2. Inclusion Criteria

Men eligible for this study satisfied the following inclusion criteria, which have been used in previous studies of prostate cancer using SEER-Medicare data[122,123] and were reviewed by experts in urology and oncology. Men in the sample received a prostate cancer diagnosis between January 1, 2000, and December 31, 2007. The year 2000 was chosen as the beginning of the sample period as the NCCN Guidelines as it marks a change in NCCN Guidelines. The 1999 NCCN Guidelines recommendation to consider "radiotherapy [in patients] post-radical prostatectomy with positive margins of high-grade disease or gross residual disease" was classified as "somewhat controversial,"[77] whereas the 2000 Guidelines recommendation that radiation therapy be considered in men with positive surgical margins was made with "uniform NCCN consensus based on lower level evidence."[167] This remained the recommendation until 2010, when the Guidelines were updated to recommend offering adjuvant or salvage radiation therapy to all patients with adverse pathologic features or detectable PSA and no evidence of disseminated disease" (Section PROS-C).[22] In this context, RT refers to external beam radiotherapy, and adverse pathologic features are positive margins, seminal vesicle invasion, extracapsular extension or detectable PSA.[22]

Figure 9. Sample Counts for Included and Excluded Observations, Aim 2



Note: SEER: Surveillance, Epidemiology and End Results; HMO: Health maintenance organization; ESRD: End stage renal disease; FFS: Fee-for-service

For men in the sample, prostate cancer was the first and only cancer diagnosis. Men diagnosed at autopsy or on their death certificate were excluded. Subjects were at least 65 years old at diagnosis and had one full year of traditional Medicare FFS eligibility (enrolled in both Part A and B) before their diagnosis (to capture comorbidities at diagnosis). Additionally, they were continuously enrolled in Medicare Parts A and B at diagnosis and for at least one year following diagnosis. Figure 9 summarizes all inclusion and exclusion criteria.

Men were alive and enrolled in a FFS plan at one year after surgery. No men with end-stage renal disease as the reason for Medicare entitlement were included, nor were those men with multiple prostate primary cancer sites or metastatic disease upon diagnosis. Among eligible men, the study focused on men who received radical prostatectomy within 180 days of diagnosis. Additionally, men who received any type of neoadjuvant therapy prior to surgery were excluded. Documentation of a qualifying surgical procedure was required in both Medicare claims (identified by billing codes presented in Table 13) and SEER data. Qualifying surgical procedures in SEER data were the following: radical prostatectomy not otherwise specified (NOS), total prostatectomy NOS, prostatectomy with resection in continuity with other organs, and prostatectomy NOS.

The sample was further refined to include only those men who met the inclusion criteria for the three clinical trials evaluating ART.[6-8] That is, they had one of the following adverse pathologic features: positive margins, seminal vesicle invasion, or extracapsular extension. One trial further limited inclusion to men who achieved an undetectable PSA level following radical prostatectomy,[6] but this cannot be captured in the SEER-Medicare data. Final sample size was 3,993 men.

Table 13. Billing Codes Used to Identify Relevant Procedures

	ICD-9	CPT/HCPCS
Radical prostatectomy	60.4, 60.5, 60.6x	55810, 55812, 55815, 55840, 55842, 55845, 00865, 55866
External beam radiation therapy*	92.24, 92.26	77301, 77305, 77310, 77315, 77321, 77371-77373, 77380, 77381, 77401, 77403-77409, 77411-77414, 77416, 77418, 77422, 77423, 77520, 77522, 77523, 77525, 77526, 0073T, G0178

*These codes capture both adjuvant and salvage/palliative radiation therapy; the distinction is made by examining treatment timing relative to radical prostatectomy.

Note: ICD-9: International Classification of Diseases, 9th Revision; CPT: Current Procedural Terminology; HCPCS: Healthcare Common Procedure Coding System

5.2.3. Construction of Agreement Variable

SEER data contain a radiation therapy variable describing the type of radiation therapy administered as a first course of treatment.[130] Radiation therapy delivered after disease progression is not captured by SEER as disease progression marks the end of initial therapy. Radiation therapy is coded as none, received (by type of radiation therapy), refused, recommended, or unknown. The possible types of radiation therapy are beam radiation, radioactive implants, radioisotopes, a combination of beam and other radiation therapy, and radiation therapy NOS. This radiation therapy variable was used to create an indicator of external beam radiation therapy (beam radiation) receipt in SEER records. Men with combination therapy and radiation therapy NOS were considered to have received beam radiation; men for whom radiation therapy was recommended (but receipt was unknown) and men who refused were considered not to have received radiation. Radioactive implants and radioisotopes were not considered as a form of ART as these modalities are not recommended adjuvant to radical prostatectomy.[22] The 29 men with unknown radiation therapy receipt were excluded.

ART was identified in Medicare claims as radiation therapy initiated within 180 days of radical prostatectomy using the billing codes in Table 13. These codes were

compiled from journal articles,[123,124] SEER-Medicare training information,[125] International Classification of Diseases, 9th revision (ICD-9) codebooks,[126,127] a Current Procedural Terminology (CPT) codebook,[128] and online Healthcare Common Procedure Coding System (HCPCS) documentation.[129] Radiation therapy delivered outside of the 180-day window following surgery was also captured in Medicare claims. Radiation therapy in this setting was considered to be salvage (delivered with curative intent in response to disease recurrence) or palliative (delivered in response to symptoms of metastatic disease), but it is not the intent of this study to distinguish between the two. The binary agreement variable was constructed to indicate whether or not there was a match in the receipt of ART across SEER and Medicare records for each individual. There were two ways in which records could not agree: either by having documentation of ART in SEER but not Medicare, or by having documentation of ART in Medicare but not SEER.

A secondary measure of agreement was constructed to test the sensitivity of results to the classification of men for whom radiation was recommended but receipt was unknown. There are two "unknown" categories within the SEER radiation therapy variable. One category is composed of men for whom radiation receipt is unknown (n = 29). These men were excluded from all analyses. The second category is men for whom radiation was recommended but it was not known whether the radiation therapy was administered (n = 41). A secondary measure of agreement was calculated after reclassifying these 41 men as having received ART.

5.2.4. Key Independent and Control Variables

Variables related to the timing of initiation of radiation therapy were hypothesized to affect the likelihood that SEER and Medicare records would match. The decision to initiate ART may not be made until after examination of the surgical specimen, so tumor and disease characteristics, specifically combined Gleason score and pathologic disease stage were examined in the analysis to identify individuals with adverse disease

features. An indicator of tumor differentiation (well/moderately differentiated versus poorly differentiated) based on collapsed Gleason categories was available for all years of data. Previous validation studies in the breast cancer literature have found differences in the likelihood of a registry-claims match by age at diagnosis,[94,96] but there is little evidence that other demographic and socioeconomic characteristics affect the likelihood that registry and claims records would agree on ART receipt. However, these characteristics may be related to disease severity as well as the type of treatment received,[68,139,140] so age at diagnosis, race/ethnicity, and marital status were included as control variables.

SEER region at diagnosis was included to control for potential differences in how well different registries capture treatment information. Surgical facility characteristics, particularly bed size and National Cancer Institute (NCI) affiliation (defined as being a clinical or comprehensive designated cancer center) were also hypothesized to affect the documentation and reporting of treatments.[96] Surgical facility characteristics were used instead of diagnosing facility characteristics as the surgical findings play a large role in the decision to initiate or recommend ART. NCI affiliation information was available only for 2002 and 2005. Assuming that affiliation status was stable, the 2002 affiliation was used for diagnoses between 2000 and 2003 and the 2005 affiliation was used for diagnoses between 2004 and 2007. Other surgical facility characteristics examined in bivariate statistical tests were medical school affiliation and the whether the facility provided therapeutic radiology services or not. A facility was classified as affiliated with a medical school if affiliation was major, limited, or graduate-level only. Other than NCI affiliation, all facility level variables were available for 2000-2007.

5.2.5. Statistical Methods

Initial descriptive analysis examined the percentage of men for whom SEER and Medicare data agree on receipt of ART as part of the initial course of treatment. These

percentages were calculated by year, SEER reporting area, patient characteristics, and surgical facility characteristics. I performed bivariate statistical tests, specifically t-tests and chi-squared tests,[154] to examine potential differences in agreement across patient characteristics.

The main analysis consisted of a person-level logistic regression in which the dependent variable was an indicator of agreement between SEER and Medicare on patient receipt of ART. I modeled this agreement as a function of a person's tumor, demographic, and surgical facility characteristics. I also estimated a second logistic regression to examine the sensitivity of results to the classification of men for whom radiation therapy was recommended but were not known to have received it. This model used the same dependent and independent variables as the primary model; agreement status differed for some men. All models were estimated with robust standard errors clustered at the surgical facility.[154] Final model specification was determined by examining each model's reported log-likelihood and Akaike Information Criterion score and individual coefficient z-statistics.[154] Results are reported in terms of odds ratios (OR) and 95% confidence intervals (CI), and statistical significance was assessed using an alpha of 0.05. I compiled data both in SAS, version 9.1 (SAS, Cary, NC) and Stata, version 10 (StataCorp, College Station, TX). I performed all data analysis in Stata. This research was approved by the Public Health-Nursing Institutional Review Board at the University of North Carolina at Chapel Hill.

5.3. Results

5.3.1. Descriptive Statistics

The average age at diagnosis for men in the sample was 69.8 years (standard deviation [SD] = 3.3) (Table 14). The sample was primarily non-Hispanic White (82.3%), with an additional 5.9% non-Hispanic Black, 6.8% Hispanic, and 4.5% of other/unknown race. Thirty-six percent of the men were diagnosed with pT2 disease (as opposed to

pT3), and most men (69.4%) had well/moderately differentiated disease, defined by a combined Gleason score of 7 or less. Approximately half of the men received surgery at a medical school-affiliated facility (54.5%), 13.4% of men received surgery at an NCI-affiliated facility, and 84.9% of men received surgery at a facility that provided radiation (although men did not necessarily receive radiation at the same facility where they received surgery).

Table 14. Sample Characteristics by Whether or Not Individual Received ART According to SEER Documentation, continued on next page

	% or mean (SD)			
	Overall	Received ART	No ART	p-value†
Number of observations	3,993	387	3,606	
Age at diagnosis (years)	69.8 (3.3)	69.5 (3.3)	69.9 (3.3)	.0273
Age categories %				.2025
65-69	53.8	58.1	53.4	
70-74	36.6	33.3	36.9	
75+	9.6	8.5	9.7	
Married at diagnosis %	82.7	83.7	82.6	.5574
State buy-in at diagnosis %	7.8	7.8	7.8	.9466
Tumor Histology %				< .0001
Well/Moderately differentiated	69.4	47.9	71.7	
Poorly differentiated	30.6	52.1	28.3	
Tumor pathologic stage %				< .0001
Stage pT2	36.1	25.3	37.3	
Stage pT3	63.9	74.7	62.7	
Race/ethnicity %				.4516
Non-Hispanic White	82.3	79.6	82.6	
Non-Hispanic Black	5.9	7.0	5.8	
Hispanic	6.8	7.2	6.7	
Other/Unknown	4.5	6.2	4.8	

*Only available for those diagnosed from 2004-2007, ** Connecticut, New Mexico, Rural Georgia, San Jose, and Atlanta registries not presented due to small cell size, † p-values obtained using t-tests and chi-square tests and apply to differences in percentages or means across columns 3 and 4.

Note: ART: Adjuvant radiation therapy; SD: Standard deviation; SEER: Surveillance, Epidemiology, and End Results; NCI: National Cancer Institute; PSA: Prostate-specific antigen; HMO: Health maintenance organization

Table 14. Sample Characteristics by Whether or Not Individual Received ART According to SEER Documentation, continued from previous page, continued on next page

	% or mean (SD)			
	Overall	Received ART	No ART	p-value†
Total Gleason score* %				< .0001
< 7	15.3	5.5	16.3	
7	61.5	45.5	63.2	
8	11.6	17.3	11.0	
> 8	11.7	31.8	9.5	
PSA value at diagnosis*	9.2 (10.0)	10.5 (11.1)	9.1 (9.9)	.0676
NCI Comorbidity Index at diagnosis	0.11 (0.26)	0.09 (0.21)	0.11 (0.26)	.0588
NCI Comorbidity categories %				.1486
0	76.6	79.6	76.3	
> 0	23.4	20.4	23.7	
Registry at diagnosis** %				.0010
San Francisco	3.3	2.8	3.3	
Detroit	7.5	8.3	7.4	
Hawaii	1.3	3.6	1.1	
Iowa	7.4	4.1	7.8	
Seattle	10.2	11.6	10.0	
Utah	7.0	7.0	7.0	
Los Angeles	12.3	14.5	12.1	
Greater California	26.3	24.8	26.4	
Kentucky	4.0	3.9	4.0	
Louisiana	5.8	7.8	5.6	
New Jersey	4.9	5.2	4.9	
Year of diagnosis %				.0374
2000	8.3	10.9	8.4	
2001	10.2	10.6	10.1	
2002	11.8	12.9	11.7	
2003	12.8	8.8	13.3	
2004	13.6	15.8	13.4	
2005	13.3	11.9	13.4	
2006	13.5	15.5	13.2	
2007	16.6	13.7	16.9	

*Only available for those diagnosed from 2004-2007, ** Connecticut, New Mexico, Rural Georgia, San Jose, and Atlanta registries not presented due to small cell size, † p-values obtained using t-tests and chi-square tests and apply to differences in percentages or means across columns 3 and 4.

Note: ART: Adjuvant radiation therapy; SD: Standard deviation; SEER: Surveillance, Epidemiology, and End Results; NCI: National Cancer Institute; PSA: Prostate-specific antigen; HMO: Health maintenance organization

Table 14. Sample Characteristics by Whether or Not Individual Received ART According to SEER Documentation, continued from previous page

	% or mean (SD)			
	Overall	Received ART	No ART	p-value†
Medicare HMO penetration rate	17.1 (15.2)	18.7 (14.9)	16.9 (15.2)	.0329
Surgical facility medical school-affiliated %	54.5	57.2	54.3	.2738
Surgical facility bed size	421 (291)	391 (263)	424 (294)	.0186
Surgical facility NCI-affiliated%	13.4	15.9	13.1	.1533
Surgical facility provides radiation %	84.9	83.6	85.1	.4448

*Only available for those diagnosed from 2004-2007, ** Connecticut, New Mexico, Rural Georgia, San Jose, and Atlanta registries not presented due to small cell size, † p-values obtained using t-tests and chi-square tests and apply to differences in percentages or means across columns 3 and 4.

Note: ART: Adjuvant radiation therapy; SD: Standard deviation; SEER: Surveillance, Epidemiology, and End Results; NCI: National Cancer Institute; PSA: Prostate-specific antigen; HMO: Health maintenance organization

Under the SEER definition of radiation receipt, only a small percentage of the sample received ART (9.7%). Using the Medicare definition of ART receipt increased this figure slightly (10.9%). Compared to men who did not receive ART, men who received ART more often had poorly differentiated disease ($p < .0001$), pT3 tumors ($p < .0001$), were slightly younger at diagnosis (69.5 years old versus 69.9, $p = .0273$), and lived in counties with higher Medicare HMO penetration (18.7% versus 16.9%, $p = .0329$). There were no significant differences across men who did and did not receive ART by surgical facility characteristics (with the exception of facility size), age at diagnosis, marital status, state buy-in, and race. Men who received ART more often received surgery in smaller hospitals than men who did not receive ART ($p = .0186$).

Overall agreement on ART receipt across the two sources was 94.8%. Across the 6 registries with reportable cell sizes, agreement was highest in the Greater California registry (95.0%) and lowest in New Jersey (92.4%). Detailed agreement by registry is not presented as the data use agreement with NCI precludes presenting data

for cell-sizes smaller than 10. Across the 15 registries with at least some variation in agreement, agreement rates ranged from 84.9% to 98.3%. Among men whose records did not agree, 53.4% had poorly differentiated tumors, compared to 29.4% of men who had agreement in their records ($p < .0001$). Men whose records did not agree were also less likely to have pT2 tumors than men whose records agreed (26.3% versus 36.7%, $p = .0012$).

Compared to men with documentation of ART in SEER but not Medicare, men with documentation of ART in Medicare but not SEER more often had poorly differentiated tumors ($p =.0404$) (Table 15). There were no other differences in the demographic, tumor, or surgical facility characteristics of men who had ART documented in one source but not the other. Men with ART documentation in Medicare only were less likely to have received surgery at an NCI-affiliated facility ($p = .0124$) than men with documentation in both sources. Men who had documentation in SEER only were less likely to be married than men with documentation in both sources ($p = .0114$).

All but 3 of the 387 men with documentation of ART receipt in SEER had documentation of radiation therapy in Medicare claims at some point beyond surgery. Of the 306 men with documentation of ART receipt in SEER and Medicare, the average time in days from surgery to first radiation therapy treatment was 106 (SD = 37, range 18-180). Of the 78 men with documentation of ART receipt in SEER and Medicare claims for radiation therapy more than 180 days after surgery (which could be either salvage or palliative rather than adjuvant), average time in days from surgery to first radiation therapy treatment was 370 (SD = 375, range 182-2,397). There were no differences in individual, tumor, or surgical facility characteristics across the two groups of men who received ART according to SEER but initiated radiation therapy according to Medicare claims either within 180 days or more than 180 days following surgery.

Table 15. Characteristics of Individuals with Record of ART in SEER Data, Medicare Data, or Both Sources, continued on next page

	% or mean (SD)			
	ART in both SEER and Medicare	ART in Medicare, not SEER	ART in SEER, not Medicare	p-value†
Number of observations	306	128	81	
Age at diagnosis (years)	69.5 (3.3)	69.6 (3.4)	69.3 (3.3)	.5243
Age categories** %				
65-69	58.8	58.6	55.6	.8095
70+	41.2	41.4	44.4	
Married at diagnosis %	86.6	82.8	72.8	.0983
State buy-in at diagnosis %	7.8	9.4	7.4	.6151
Tumor Histology %				
Well/Moderately differentiated	45.9	40.9	55.6	
Poorly differentiated	54.1	59.1	44.4	.0404
Tumor pathologic stage %				
Stage pT2	24.2	24.2	29.6	.3965
Stage pT3	75.8	75.8	70.4	
Race/ethnicity** %				.9424
Non-Hispanic White	78.8	80.5	82.7	
Other/Unknown	21.2	19.5	17.3	
PSA value at diagnosis*	10.7 (11.8)	14.0 (18.6)	9.8 (7.0)	.1264
NCI Comorbidity categories %				.2347
0	78.8	75.8	82.7	
> 0	21.2	24.2	17.3	
NCI Comorbidity Index at diagnosis	0.09 (0.21)	0.12 (0.30)	0.08 (0.23)	.2747

*Only available for those diagnosed from 2004-2007, **Categories collapsed due to small cell-size. Gleason score and registry at diagnosis not presented due to small cell size. † p-values obtained using t-tests and chi-square tests and apply to differences in percentages or means across columns 3 and 4.

Note: ART: Adjuvant radiation therapy; SD: Standard deviation; SEER: Surveillance, Epidemiology, and End Results; NCI: National Cancer Institute; PSA: Prostate-specific antigen; HMO: Health maintenance organization

Table 15. Characteristics of Individuals with Record of ART in SEER Data, Medicare Data, or Both Sources, continued from previous page

	% or mean (SD)			
	ART in both SEER and Medicare	ART in Medicare, not SEER	ART in SEER, not Medicare	p-value†
Year of diagnosis** %				.7464
2000 or 2001	22.1	23.4	18.4	
2002	12.8	10.9	13.6	
2003	7.5	8.6	13.6	
2004	16.0	11.7	14.8	
2005	11.8	9.4	12.4	
2006	15.4	18.8	16.1	
2007	14.4	17.2	11.1	
Medicare HMO penetration rate	18.4 (14.9)	19.4 (15.0)	19.7 (15.1)	.8850
Surgical facility medical school-affiliated %	58.3	54.4	53.1	.8545
Surgical facility bed size	395 (264)	404 (228)	375 (260)	.4019
Surgical facility NCI-affiliated%	17.2	8.8	11.1	.5949
Surgical facility provides radiation %	84.4	86.4	80.2	.2573

*Only available for those diagnosed from 2004-2007, **Categories collapsed due to small cell-size. Gleason score and registry at diagnosis not presented due to small cell size. † p-values obtained using t-tests and chi-square tests and apply to differences in percentages or means across columns 3 and 4.

Note: ART: Adjuvant radiation therapy; SD: Standard deviation; SEER: Surveillance, Epidemiology, and End Results; NCI: National Cancer Institute; PSA: Prostate-specific antigen; HMO: Health maintenance organization

5.3.2. Multivariate Logistic Regression Analysis

The relationship between SEER and Medicare record agreement and tumor, individual, and surgical facility characteristics was more fully explored in a logistic regression model. The final model specification did not variables indicating whether the surgical facility was affiliated with a medical school or provided radiation therapy as these variables were not shown to affect agreement in the bivariate analyses and their inclusion did not improve model fit. Year of diagnosis was included as a continuous

variable to detect a potential trend in agreement over time and to preserve degrees of freedom.

Men with poorly differentiated tumors had lower odds of agreement than men with well- or moderately-differentiated tumors (OR = 0.38, 95% CI = 0.28-0.52), but pathologic stage did not have a significant effect on the odds of record agreement (Table 16). As a group, registry at diagnosis had a significant effect on the odds of agreement (χ^2 = 41.22, p = .0002), and individual registries varied in whether they had higher or lower odds of agreement than the reference category (Greater California). Significantly, men diagnosed in Utah had higher odds of agreement (OR = 2.72, 95% CI = 1.06-6.90). Men diagnosed in Hawaii registry area had lower odds of agreement (OR = 0.26, 95% CI = 0.13-0.53), as did men diagnosed in the Los Angeles registry area (OR = 0.54, 95% CI = 0.32-0.91). Receiving surgery at an NCI-affiliated facility was associated with higher odds of agreement (OR = 1.85, 95% CI = 1.02-3.37).

Table 16. Logistic Regression Results for Agreement Between SEER and Medicare

	Regression Results	
	OR	95% CI
Age at diagnosis	1.05*	1.00-1.10
Race (non-Hispanic White is reference)		
Non-Hispanic Black	1.26	0.64-2.48
Hispanic	0.95	0.54-1.66
Other/Unknown	1.90	0.98-3.68
Pathologic stage T2	1.28	0.90-1.83
Tumor poorly differentiated	0.38**	0.28-0.52
Registry at diagnosis (Greater California is reference)†		
San Francisco	0.96	0.42-2.14
Connecticut	1.03	0.47-2.23
Detroit	0.74	0.37-1.49
Hawaii	0.24**	0.13-0.47
Iowa	2.63	0.80-8.58
New Mexico	0.82	0.63-1.84
Seattle	0.98	0.56-1.71
Utah	2.72*	1.07-6.90
Atlanta	0.69	0.16-2.99
San Jose	0.88	0.49-1.59
Los Angeles	0.54*	0.32-0.91
Kentucky	0.62	0.24-1.63
Louisiana	1.58	0.67-3.75
New Jersey	0.58	0.31-1.08
HMO penetration rate	0.64	0.19-2.16
Bed size	1.06	0.99-1.13
NCI affiliation	1.85*	1.02-3.37
Year of diagnosis	0.98	0.91-1.05
Observations	3,929	
Log pseudolikelihood	-754.03	
AIC	1558.07	

* significant at 5%, ** significant at 1%, †Rural Georgia registry area dropped due to perfect prediction, standard errors clustered by surgical facility

Note: SEER: Surveillance, Epidemiology, and End Results; NCI: National Cancer Institute; OR: odds ratio; CI: confidence interval; AIC: Akaike Information Criterion

Table 17. Logistic Regression Results for Agreement Between SEER and Medicare, Alternate SEER Radiation Definition

	Regression Results	
	OR	95% CI
Age at diagnosis	1.05*	1.00-1.10
Race (non-Hispanic White is reference)		
Non-Hispanic Black	1.08	0.61-1.89
Hispanic	1.06	0.62-1.82
Other/Unknown	2.18*	1.12-4.24
Pathologic stage T2	1.27	0.92-1.75
Tumor poorly differentiated	0.39**	0.29-0.51
Registry at diagnosis (Greater California is reference)†		
San Francisco	1.08	0.50-2.37
Connecticut	0.88	0.44-1.75
Detroit	0.77	0.41-1.45
Hawaii	0.26**	0.14-0.50
Iowa	2.89*	1.00-8.30
New Mexico	0.93	0.42-2.08
Seattle	0.97	0.60-1.56
Utah	3.22*	1.30-7.95
Atlanta	0.89	0.20-3.99
San Jose	0.87	0.46-1.64
Los Angeles	0.59*	0.37-0.93
Kentucky	0.95	0.42-2.17
Louisiana	2.09	0.91-4.80
New Jersey	0.80	0.44-1.46
HMO penetration rate	0.76	0.23-2.48
Bed size	1.02	0.97-1.08
NCI affiliation	1.33	0.88-2.02
Year of diagnosis	0.97	0.91-1.04
Observations	3,929	
Log pseudolikelihood	-831.95	
AIC	1713.91	

* significant at 5%, ** significant at 1%, †Rural Georgia registry area dropped due to perfect prediction, standard errors clustered by surgical facility

Note: SEER: Surveillance, Epidemiology, and End Results; NCI: National Cancer Institute; OR: odds ratio; CI: confidence interval; AIC: Akaike Information Criterion

To test the sensitivity of the results to the specification of the SEER radiation variable, an alternate measure of ART receipt in SEER data was examined. An

additional logistic model was estimated to test the sensitivity of the results to the assumption that the 41 men for whom radiation therapy was recommended did not receive ART (Table 17). In the model presented in Table 16, these men were considered not to have documentation of radiation therapy in SEER. In the model presented in Table 17, these 41 men were considered to have received ART according to SEER data (following the example of an earlier examination of ART receipt in SEER data[86]).

The magnitudes of the estimated ORs in the models presented in Table 16 and Table 17 are similar, but there are some differences in which variables have a significant effect on the odds of agreement. Specifically, the odds ratio associated with receiving surgery at an NCI-affiliated facility was no longer significant, but men of other/unknown race had higher odds of agreement (OR = 2.17, 95% CI = 1.12-4.24). Of the 41 men with recommended but unknown radiation receipt in SEER, 20 had no Medicare claim for radiation therapy at any point in time. The remaining 21 men had Medicare claims for radiation therapy, with average time from surgery to initiation of radiation therapy of 540 days (SD = 478, range = 73-1,533).

5.4. Discussion

Agreement between SEER and Medicare with regards to ART receipt was found to be high, at 94.8%. This is slightly higher than the 93% agreement among prostate cancer patients reported by Virnig et al. in their 2002 study.[34] These rates cannot be directly compared, however, as the first study sought to document agreement for all prostate cancer patients and all types of radiation and the present study examined the subset of men who received a radical prostatectomy and external beam radiation therapy adjuvant to radical prostatectomy. The differences in samples across the two studies make it impossible to say with certainty whether there has been an improvement in SEER radiation documentation since the mid-1990s.

Overall, 434 men had documentation of ART receipt in Medicare (10.9%), and 387 men had documentation of ART receipt in SEER (9.7%). These percentages are comparable to the 13.5% of men with qualifying disease characteristics for whom radiation therapy was recommended reported in an earlier study of ART receipt in SEER.[86] The rates of ART found in this study are, however, lower than the 18.2% reported in a second study of ART receipt in SEER.[87] These previous studies used the entire SEER population rather than only those men participating in Medicare plans, so differences in sample characteristics may help explain some of the difference in reported receipt of ART.

Among men with documentation of ART in SEER but not Medicare, almost all of the disagreement is driven by the timing of radiation therapy. In recent clinical trials, ART was delivered within 16 weeks of surgery,[7,9] and the 180-day (i.e. 6-month) period used in this study was designed as an upper bound on the window of time in which radiation could be considered adjuvant to surgery (as opposed to salvage or palliative). Since almost all men with documentation of ART in SEER also have documentation of radiation in Medicare at some point after surgery, the rate of agreement in receipt of ART is almost entirely dependent on the time interval used to differentiate adjuvant and salvage or palliative radiation. The use of SEER records alone to measure ART would result in erroneously classifying men who received salvage or palliative radiation therapy as receiving ART. On the other hand, use of Medicare records alone could result in erroneously classifying men who received salvage radiation therapy as receiving ART. In some men, radiation therapy delivered within 180 days of radical prostatectomy could be initiated in response to rising PSA levels following surgery. Radiation therapy for these men would be considered salvage, not adjuvant, but there is no way to capture this in Medicare claims data.

The results from both regression models suggest that Medicare and SEER are less likely to agree on receipt of ART for men with more severe disease. In bivariate analyses, men with pT3 tumors and poorly-differentiated tumors are less likely to have agreement in SEER and Medicare on whether or not they received ART, but only tumor differentiation significantly affected agreement in multivariate regression analyses. This suggests that SEER records alone are insufficient for classifying men according to receipt of ART, particularly when the sample of interest is men for whom ART is most likely to be recommended and initiated.

I also found evidence of differences across registries in agreement on ART receipt. In both regressions, the registry construct had an overall significant effect on agreement, and the individual registry results were robust across ART receipt specifications. Specifically, the men living in the Utah registry area had higher odds of record agreement compared to men in the Greater California registry area, and men living in the Hawaii and Los Angeles registry areas had lower odds of record agreement. Utah and Hawaii entered the SEER program in 1973, and Los Angeles entered the SEER program in 1992,[119] so the difference in agreement does not appear to be related to how long the registry has been established.

The findings from this study are applicable to only a portion of prostate cancer patients, those who were continuously enrolled in traditional FFS Medicare throughout the study period. The use of Medicare claims, though essential to fulfilling the aim of this study, limits the generalizability of the results beyond the study population. Because private insurance plans used by traditional FFS and Medicare HMO enrollees may differ in their documentation and reimbursement policies, these differences could affect the rate of ART receipt observed in different insurance group populations. That is, it is unclear whether the findings from this study would extend to patient populations without Medicare coverage or with Medicare HMO coverage. Also, enrollment in Medicare

managed care plans is elective, so there is the possibility of selection bias in the study population. The county-level proportion of Medicare eligible enrolled in HMO plans was included in models to attempt to control for possible selection bias.

Increasing focus on the added survival benefit conferred by ART for some men has already created interest in examining the receipt of ART in the SEER population.[86,87] This study suggests that the rates of receipt reported in examinations of the SEER population may be slight overestimates, as there were more men receiving salvage or palliative radiation therapy classified as ART in SEER than there were men with ART Medicare claims but no documentation of ART in SEER. However, agreement between the two sources was very high overall, which confirms a previous comparison of radiation receipt in prostate cancer patients.[34] This high agreement, combined with the low rates of ART observed in the sample, suggests that the low rates of ART reported by previous studies of SEER data are unlikely due to underreporting of radiation therapy in SEER. Rather, the prior findings are likely due to lack of adoption of ART in response to recently reported clinical trial results. High agreement notwithstanding, neither Medicare nor SEER alone can be considered the gold standard in studying treatment, and this study calls attention to potential sources of bias in the use of SEER data to examine ART receipt, particularly in the sample of men for whom ART is most likely to be recommended.

CHAPTER 6. THE COST-UTILITY OF ADJUVANT RADIATION THERAPY FOLLOWING RADICAL PROSTATECTOMY

6.1. Introduction

Of prostate cancer patients presenting with pathological stage T3 (pT3) disease, 10% to 50% may not achieve disease control with radical prostatectomy alone.[75] In 2005, the initial publication of results from the first of three major clinical trials evaluating the use of adjuvant radiation therapy (ART) after prostatectomy provided evidence of the benefit of ART for certain high-risk prostate cancer patients.[7] The other two trials published similar results in 2006 and 2009.[6,8] In all three trials, ART was compared to a wait and see approach in which salvage radiation therapy (SRT) was initiated in response to disease recurrence, as indicated by increasing prostate-specific antigen (PSA) levels or detected through biopsy. This time period also saw the publication of a large retrospective study reporting durable disease response to SRT following prostatectomy.[76]

The clinical trial results suggest benefits associated with ART in terms of time to PSA recurrence, but the associated harms are unclear. On one hand, treating all qualifying patients with ART would result in treating individuals who would have lived recurrence-free without additional treatment. As the side effects of radiation therapy can have serious quality of life implications,[10-13] the impact of radiation therapy on these patients and the associated costs should be carefully considered. On the other hand, the success of the wait and see approach is predicated upon frequent PSA testing and appropriate follow-up care in the event of a detectable and rising PSA. The analysis in Chapter 4 demonstrates that PSA surveillance rates decrease over time and are lower in

minority populations, which indicates that some men may be at risk of delayed detection of disease recurrence.

Only one of the three trials has reported improved overall survival associated with ART compared to the wait and see approach (13.3 versus 15.2 years),[9] however, this study enrolled patients prior to widespread PSA screening and questions have been raised with respect to the generalizability of this study cohort to contemporary men with screen-detected disease.[81] However, even if the evidence supporting one approach over the other is clear in terms of survival, it is important to consider quality of life associated with each approach to radiation therapy. The Institute of Medicine states that the late effects on quality of life of both treatment for local disease and living with recurrent disease are of central importance to prostate cancer survivors.[47] As the combination of surgery and radiation therapy, administered as either adjuvant or salvage therapy, may result in additional decrements in health-related quality of life beyond those associated with a single treatment,[168] patients and physicians must weigh changes in quality of life against the potential for improved survival. As the findings presented in Chapter 4 indicate, PSA surveillance rates are high in the year immediately following radical prostatectomy, but surveillance drops off over time. Additionally, minority racial groups are at greater risk for not receiving surveillance in concordance with established guidelines. Low surveillance rates could be associated with decreased detection of disease recurrence, which could be a mechanism to help explain observed racial disparities in prostate cancer outcomes.

The present model extends and improves upon a recent decision analysis comparing the quality of life benefits of ART to a wait and see approach to radiation therapy after radical prostatectomy.[118] The authors found that the wait and see approach resulted in 6.8 quality-adjusted life-years (QALYs) during a 10-year period compared to 6.13 QALYs for ART. However, ART was found to be more effective than the wait and

see approach in terms of 10-year PSA recurrence-free survival, metastasis-free survival, and overall survival. The present model improves upon this existing model by evaluating the lifetime costs and effects of the two approaches, evaluating results using a full probabilistic sensitivity analysis, discounting future costs and time, and more precisely specifying possible transitions within each period.

The long natural history of prostate cancer, combined with advances in detection and treatment, make it difficult to evaluate long-term outcomes using prospective studies. Cost-utility and cost-effectiveness models provide one way to estimate and to simulate how changing practice patterns and treatment recommendations could affect a range of outcomes, including survival and quality of life. This approach is ideal for evaluating outcomes associated with post-operative radiation therapy in prostate cancer, as factors that may influence the effectiveness of one approach over another (such as intensity of post-surgical PSA surveillance) were not considered in clinical trial evaluation of treatment efficacy.

6.2. Methods

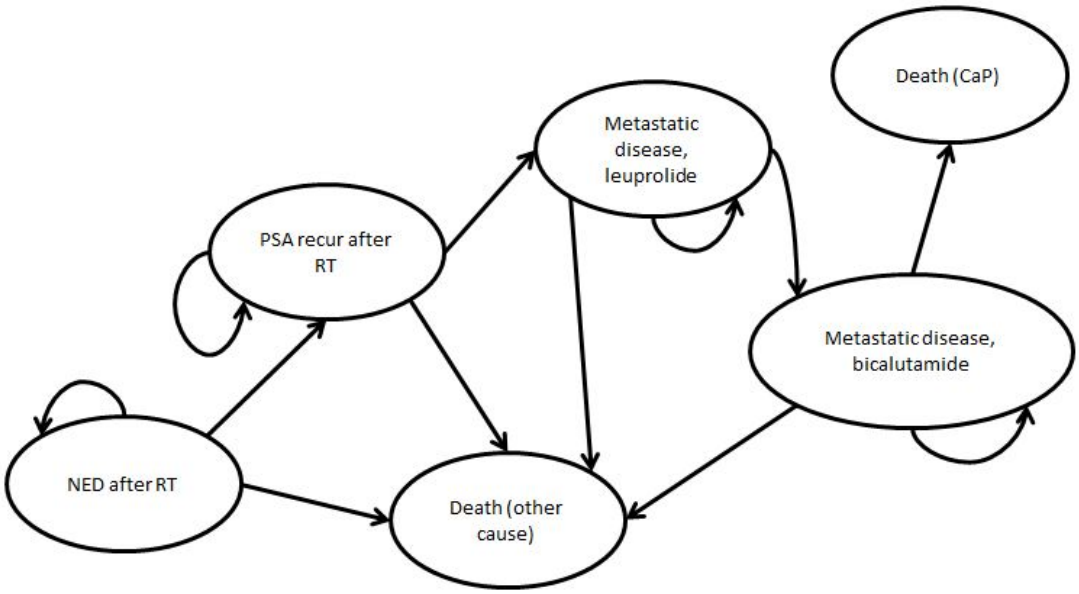
6.2.1. Model Construction

A Markov model was constructed to estimate the cost-utility of the current wait and see approach to SRT compared to an alternative policy of ART within four months of prostatectomy for a cohort of patients. The hypothetical model cohort was composed of men 65 years old treated with radical prostatectomy for high-risk prostate cancer within 180 days of biopsy-proven diagnosis. Following the inclusion criteria of the clinical trials, high-risk disease was defined as a pathological T3 tumor or a pathological T2 tumor with positive surgical margins. All men were assumed to have achieved an undetectable PSA level following surgery (< 0.1 ng/ml).

Figure 10 shows the Markov model structure depicting the approach of ART for all qualifying patients. See Figures 11 and 12 for the complete model. In each cycle of

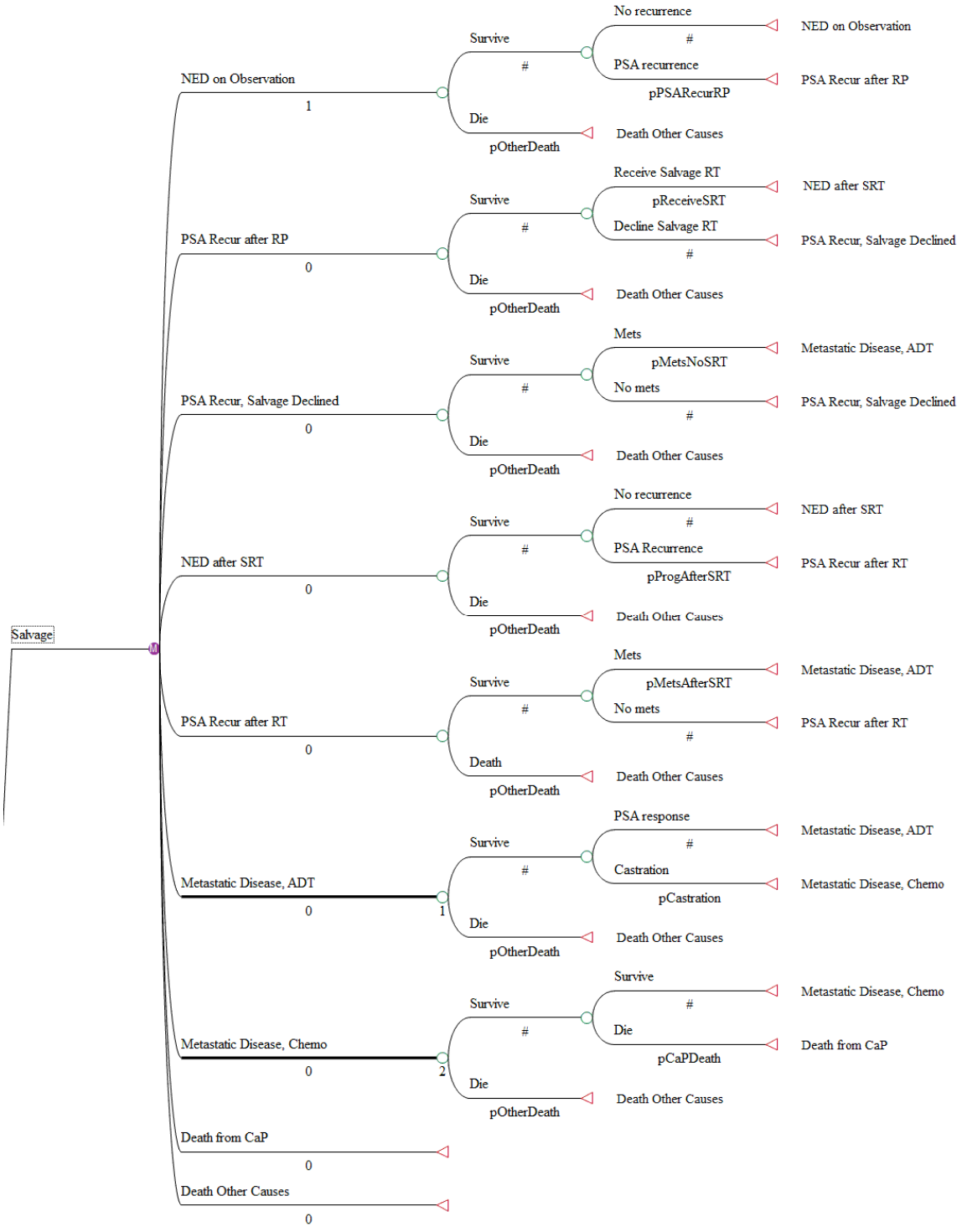
the model, defined as three months, individuals may move from their current disease state to a new one or remain in their current disease state. For example, in Figure 10, all individuals enter the model in period one in the state “NED (no evidence of disease) after RT.” At the end of 3 months, they either remain in this state or experience a PSA recurrence without metastatic disease (“PSA Recur after RT”). In this way, all individuals move through the model until they end in an absorbing state, that is, one that does not allow outward movement. In this model, absorbing states include death from prostate cancer (“Death, CaP”) or death from other causes (“Death, other cause”). Individuals may transition into death from other causes from any state in the model (other than death from prostate cancer) at any time, whereas individuals may transition to death from prostate cancer only after having developed metastatic disease. This model contains two states of metastatic disease: metastatic disease responsive to hormonal therapy and metastatic disease resistant to hormonal therapy (hormone-refractory disease). Men in these two states of metastatic disease receive different treatments, and hormone-refractory disease is associated with greatly reduced quality of life compared to metastatic disease that is responsive to hormonal therapy.

Figure 10. Markov Cohort Model for Adjuvant Radiation Therapy Treatment Arm



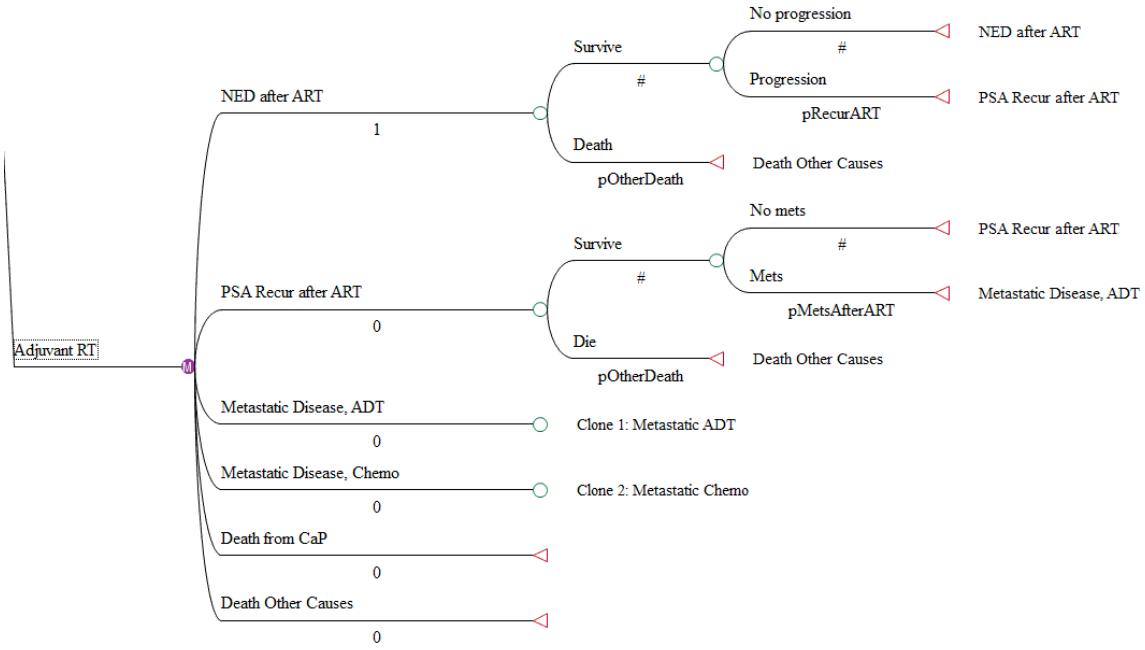
Note: NED: No evidence of disease; PSA: Prostate-specific antigen; CaP: Prostate cancer; RT: Radiation therapy

Figure 11. Wait and See Arm of Markov Model



Note: PSA: prostate-specific antigen; Chemo; chemotherapy (bicalutamide)SRT: salvage radiation therapy; RP: radical prostatectomy; NED: no evidence of disease; CaP: prostate cancer; ADT: androgen deprivation therapy (leuprolide); RT: radiation therapy; Mets: metastatic disease

Figure 12. Adjuvant Radiation Therapy Arm of Markov Model



Note: PSA: prostate-specific antigen; Chemo; chemotherapy (bicalutamide)SRT: salvage radiation therapy; RP: radical prostatectomy; NED: no evidence of disease; CaP: prostate cancer; ADT: androgen deprivation therapy (leuprolide); RT: radiation therapy; Mets: metastatic disease; Clone 1 and 2 - refer to Figure 11.

6.2.2. Probabilities

Cost-utility, cost-effectiveness, and comparative effectiveness studies, along with results from clinical trials and retrospective series were used to derive transition probabilities for the model (Table 18). A PubMed search was conducted using the following terms alone and in combination: prostate cancer, cancer, quality of life, utility, cost-effectiveness, cost-utility, QALY, willingness to pay, quality of life, comparative effectiveness, and health-related quality of life. This search process began in May 2011, and was periodically repeated between May and December 2011 to capture any new publications. I reviewed reference lists from relevant articles to identify additional sources of input data.

Table 18. Probabilities, Utilities, and Costs Used in Base-case and One-way Sensitivity Analysis, continued on next page

Probabilities	Base-case value	SD	Lower 95% CI	Upper 95% CI	Distribution
Adverse effects of treatment[112]					
Short term					
Radical prostatectomy					
Sexual	0.768	0.054	0.662	0.874	Beta
Urinary	0.467	0.110	0.251	0.683	Beta
Radiation therapy					
Urinary	0.300	0.086	0.134	0.469	Beta
Bowel	0.184	0.052	0.082	0.286	Beta
Long term					
Radical prostatectomy					
Sexual	0.453	0.034	0.386	0.520	Beta
Urinary	0.127	0.016	0.096	0.158	Beta
Radiation therapy					
Urinary	0.134	0.030	0.075	0.193	Beta
Bowel	0.066	0.014	0.039	0.093	Beta
Sexual	0.485	0.048	0.391	0.579	Beta
Progression-related					
Progression following RP[6]	0.46	0.046	0.370	0.550	Beta
Receipt of SRT after recurrence	0.75		0	1	NA
Progression following SRT[5]	0.45	0.11	0.234	0.667	Beta
Progression following ART[6]	0.28	0.209	0.351		Beta
Metastases following progression[4]	0.37	0.299	0.441		Beta
Development of metastatic disease no longer responsive to hormonal therapy[143]	0.35	0.049	0.254	0.446	Beta
Death from prostate cancer[144]	0.39	0.059	0.274	0.506	Beta
Death from other causes[145]	Varied				NA

Cost (in 2011 US$)	Base-case value	SD	Lower 95% CI	Upper 95% CI	Distribution	Units
Bone Scan[141]	261	71.14	122	400	Log Normal	1
IMRT[141]						
IMRT Visit	183	35.24	114	252	Log Normal	2
CT Scan	198	57.16	86	310	Log Normal	1
IMRT Planning	2,150	218.41	1,721	2,578	Gamma	1
IMRT Delivery	537	61.51	416	657	Gamma	37
Leuprolide[142]	314	49.30	217	411	Gamma	2 per month
Bicalutamide[142]	1,881	66.57	1,751	2,011	Gamma	per 100 days
Utilities[148]	**Base-case value**	**SD**	**Lower 95% CI**	**Upper 95% CI**	**Distribution**	
Impotence	0.89	0.16	0.576	1	Beta	
Urinary incontinence	0.83	0.21	0.418	1	Beta	
Bowel problems	0.71	0.26	0.200	1	Beta	
Impotence and urinary incontinence	0.79	0.23	0.339	1	Beta	
Urinary incontinence and bowel problems	0.7	0.26	0.190	1	Beta	
Impotence and bowel problems	0.57	0.26	0.060	1	Beta	
Impotence, urinary incontinence, and bowel problems	0.45	0.31	0.050	1	Beta	
Metastatic disease responsive to leuprolide[149,150]	0.47	0.3	0.050	1	Beta	
Metastatic disease not responsive to leuprolide	0.25	0.11	0.034	0.466	Beta	

Note: SD: standard deviation; IMRT: intensity-modulated radiation therapy, CT: computed tomography; RP: radical prostatectomy; SRT: salvage radiation therapy; ART: adjuvant radiation therapy; NA: not applicable; CI: confidence interval

Probabilities associated with biochemical recurrence following radical prostatectomy and biochemical recurrence following ART came from two recent clinical trials.[6,78] Probabilities for progression from disease recurrence to metastatic disease and progression from hormonally responsive metastatic disease to hormone-refractory disease came from retrospective studies,[4,5,83,143] and biochemical recurrence following SRT and survival following hormone-refractory disease were calculated using peer-reviewed risk prediction nomograms.[5,144] When available, event counts were used to create beta distributions around the base-case probability. If event counts were not presented in the source article, a beta distribution was approximated from a mean and standard deviation.[100] All probabilities were converted from annual or multiple year probabilities to quarterly probabilities.[100] Annual probability of death from background causes was obtained from the 2007 U.S. life tables for men.[145]

In the base-case, 5-year probability of progression-free survival following radical prostatectomy in the wait and see arm was 0.54.[6] This probability is equivalent to an annual progression probability of 0.116. Following progression, 75% of men were assumed to receive SRT.[118] The probability of disease progression following SRT was calculated using a peer-reviewed risk prediction nomogram[5] populated with disease characteristics of men in the clinical trial conducted by the German Cancer Society (referred to hereafter as ARO) and two retrospective studies of SRT.[5,6,83] In contrast to the clinical trial results, which were presented in terms of the 5-year probability of progression-free survival, the nomogram output is the 6-year probability of progression-free survival. Specifically, the 6-year progression-free probability for a man with a pre-prostatectomy PSA of 10 ng/ml, a primary Gleason score of 3 with a secondary Gleason score of 4, positive surgical margins, extracapsular extension, PSA recurrence 12 months after prostatectomy, and a PSA doubling time of 5 months who received a radiation dose of 66 gray (Gy) at a PSA level of 0.5 ng/ml was estimated at 0.55, which

is equivalent to an annual progression probability of 0.095. A standard deviation of 0.11 (20% of the 6-year estimate) was assumed and used to create a beta distribution. The probability of progression varies based on the PSA level at initiation of SRT, and the nomogram was repopulated for cohorts of men receiving SRT at different PSA levels. These progression probabilities were used in scenario analyses. Additional distributions were created around the nomogram-calculated probability of progression when SRT was initiated at PSA levels of 0.1 ng/ml, 1 ng/ml, 1.5 ng/ml, and 3 ng/ml.[5]

The 5-year probability of progression-free survival in the ART arm was 0.72 (95% CI 0.65-0.81),[6] equivalent to an annual progression probability of 0.064. Once biochemical recurrence occurred following radiation therapy, whether adjuvant or salvage, the annual probability of progressing to metastatic disease was 0.088.[4] This probability also was used for men who progressed after radical prostatectomy but did not receive SRT.

Additional probabilities of disease progression following radical prostatectomy, ART, and SRT were derived for subgroups of men with and without positive surgical margins and with and without seminal vesicle invasion. These subgroup probabilities are presented in Table 19.

The probabilities for developing short- and long-term urinary, sexual, and gastrointestinal adverse effects following radical prostatectomy and radiation therapy came from a random-effects meta-analysis conducted by Hayes et al.[112] Short-term adverse events resolved within 3 months of treatment, whereas long-term adverse events persisted from 3 months until death. Following the methods of Elliot et al.,[118] the probabilities of developing adverse events were considered to be the probability of developing the given adverse event alone and in combination with other adverse events.

Table 19. Probabilities of PSA Recurrence by Tumor Characteristics

	ART			WS			SRT
	Patients with PSA Recurrence	Total Patients	Equivalent 5-Year Probability of Recurrence	Patients with PSA Recurrence	Total Patients	Equivalent 5-Year Probability of Recurrence	6-Year Probability of Recurrence[5]
Surgical Margins[6]							
Negative	13	48	0.27	19	61	0.31	0.64
Positive	25	100	0.25	47	97	0.49	0.50
Seminal Vesicle Invasion[6]							
No	14	99	0.14	36	101	0.36	0.50
Yes	19	40	0.48	24	43	0.56	0.58

Note: ART: adjuvant radiation therapy; WS: wait and see; SRT: salvage radiation therapy; PSA: prostate-specific antigen

6.2.3. Utilities

Substantial research exists on prostate cancer-related quality of life and health states.[146] Titles and abstracts located through the PubMed searches were reviewed to identify articles that reported utility values rather than quality of life or functioning scores. Although many instruments are used to evaluate quality of life in prostate cancer patients,[147] few of these instruments generate utility measures. Many of the articles identified in the initial search were cost-effectiveness or cost-utility studies that referenced utility values from a previous study, so reference lists of relevant articles were reviewed to identify any additional publications.

Thirty studies were used to create a database of prostate cancer-specific utility values containing 289 utility values. Values were categorized as describing a treatment state, adverse event, short-term effect, and/or long-term effect. The quality of each measure and its relevance to the current study were evaluated by examining the population from which the value was elicited, the elicitation technique, the sample size, and the utility scale endpoints. Utilities from scales using anchors other than death and perfect health were excluded. Utility values derived from expert opinion also were excluded unless they were the only ones representing a specific health state. To ensure the consistency of the evaluated outcomes, studies were excluded if cancer patients were asked to evaluate the utility of their current health state rather than a standard health state description.

Seventeen of the studies presenting prostate cancer-related utilities involved utilities related to metastatic disease. Of these 17 studies, seven met the inclusion criteria described above, however 3 studies appeared to use the same data set, bringing the total number of studies with useful utility data to 5.[113,115,148-150] Two of these 5 studies reported more than one utility measure.[149,150] Since the model had two metastatic disease states, utilities were separated by whether or not the disease was responsive to

hormonal therapy (specifically, leuprolide). In cases where the authors did not specifically state the level of disease advancement, the disease description used in the utility exercise was used to properly categorize the utility. This process resulted in a final group of 4 estimates from 2 studies for the utility of living with metastatic prostate cancer responsive to hormonal therapy[149,150] and 7 utility estimates from 5 studies for the utility of living with metastatic prostate cancer that is no longer hormonally responsive.[113,115,148-150] For hormonally responsive disease, the utility value mean and standard deviation were determined by examining the means, standard deviations (where available), and interquartile ranges (where available) to derive a single mean and standard deviation reflective of the ranges reported in the two studies. For metastatic disease no longer responsive to hormonal therapy, the base-case utility value mean and standard deviation were taken from Stewart et al.[148] as this study focused specifically on the preferences of men aged 60 and older, used the standard gamble technique (which, all else equal, is preferred to the time trade off technique for preference elicitation[102]), and falls in the middle of the range of utilities reported in the five studies.

The utilities associated with living with adverse events related to treatment were taken from Stewart et al.[148] In contrast to other utility studies that examine the utilities of adverse events separately, Stewart et al. elicited utilities for adverse events singularly and in combination. These combinations are essential for evaluating health states following prostate cancer treatment, as individuals may experience multiple treatment-related adverse events, and no model exists to accurately predict joint health state utilities from the component single health state utilities.[151] Table 18 presents all utility values used in the analysis.

6.2.4. Costs

With the exception of drug costs, all cost data for the analysis were derived from established Medicare fee schedules (Table 18). Costs were from the calendar year 2011

fee schedule,[141] which is based on Healthcare Common Procedure Coding System (HCPCS) codes. As the difference in salvage and adjuvant radiation therapy is only in the timing of the treatment rather than the dosage or administration, both arms of the model incorporate essentially the same costs. The model did not include costs associated with radical prostatectomy or surgical follow-up, as all individuals experienced this procedure prior to the beginning of the model. Included costs are those costs associated with radiation therapy administration and follow-up and management of metastatic disease.

Metastatic disease was assumed to be initially treated with gonadotropin-releasing hormone agonist (leuprolide) rather than orchiectomy, and hormone-refractory disease was assumed to be treated with bicalutamide. Drug prices were obtained from the 2010 edition of the *Red Book*[142] and adjusted to 2011 dollars using the medical care-specific Consumer Price Index.[99,152] All individuals were assumed to receive semi-annual PSA tests regardless of timing of radiation receipt based the analysis presented in Chapter 4, so this cost excluded. As the adverse events included in the model were considered to be minor rather than requiring substantial medical intervention, there were no additional direct healthcare costs associated with adverse events.

The Centers for Medicare and Medicaid Services provides information on both the national payment amount and Part B carrier-specific payment amounts. The national payment amount was used in the base-case analysis, and the carrier-specific amounts were used to create a distribution for probabilistic analysis. Input Analyzer (Arena Version 13.9, Rockwell Automation, Inc., Wexford, PA) was used to analyze the entire set of payment amounts and create distributions to best fit the data.

All costs and outcomes occurring in the future were discounted at 3% per year to account for the time value of money and utility.[102,156] All results are presented from the

payer perspective (in this case, Medicare) over the time horizon from prostatectomy to death, which, on average, occurred approximately 15 years after radical prostatectomy.

6.2.5. Analysis

The model was used to calculate the total cost and the total utility associated with the ART approach and the total cost and the total utility associated with the wait and see approach. In addition, the proportion of the cohort experiencing disease recurrence, receiving radiation therapy, developing metastatic disease, and dying from prostate cancer were calculated for each alternative. The total cost and total utility totals were used to calculate the incremental cost-effectiveness ratio:

$$ICER = (Cost_{(adjuvant)} - Cost_{(wait\ and\ see)})/(Benefit_{(adjuvant)} - Benefit_{(wait\ and\ see)})$$

The ICER either will be positive or negative, and the interpretation of the ICER can most easily be seen by plotting the incremental costs (y-axis) and benefits (x-axis) on an x-y axis (called the incremental cost-effectiveness plane). The ICER is the slope of the line from the origin to the point. When the point estimate ICER falls in northwest or southeast quadrants, one alternative is clearly superior to the other.[102] Points (and therefore ICER values) falling in northeast or southwest quadrants represent alternatives with a trade-off between cost and effectiveness. The standard practice is to establish a threshold for the maximum willingness to pay (WTP) per QALY.[102] The slope of a line running through the origin of the x-y axis represents this WTP threshold. An ICER above the threshold indicates the superiority of the wait and see approach to salvage radiation therapy, whereas an ICER below the threshold indicates the superiority of ART. Generally, in the U.S., an intervention or program is considered cost-effective if the ICER is less than $50,000 per QALY.[103]

Clearly, a single estimate of the ICER is insufficient for drawing conclusions about the relative costs and benefits of the two approaches to radiation therapy. Although a single estimate for each parameter was chosen for the base-case scenario,

one-way and probabilistic sensitivity analyses were used to test the sensitivity of the results to uncertainty in each parameter.[102]

In one-way sensitivity analyses, one parameter at a time was varied over its range of plausible values (Table 18) to determine how much influence that single parameter had on the ICER.[102] Parameters that have a large influence on the ICER, particularly ones that cause the ICER to move from one quadrant to another, indicate areas in which more information would be most valuable. That is, narrowing down the range of values that parameter might take would lead to a more concise estimate of each alternative's relative value.[102]

In the probabilistic sensitivity analysis, all parameters are varied simultaneously.[102] Whereas the one-way sensitivity analysis requires only a range for each parameter, the probabilistic sensitivity analysis requires both a range and a defined distribution.[102] The distributions associated with each variable are given in Table 18. All probabilities are estimated from a binomial proportion, thus beta distributions are assumed.[100] The distributions for the Medicare cost parameters were created from the source data,[141] which indicated that the lognormal and gamma distributions were the best fit. The use of these distributions is supported by the skewed nature of cost data.[100] The 2010 *Red Book* provided 8 prices for bicalutamide and 4 prices for leuprolide,[142] which were used to calculate means and standard deviations. The method of moments approach was then used to create gamma distributions from the means and standard deviations.[100]

The probabilistic sensitivity analysis used a Monte Carlo simulation of 1,000 iterations which selected the values of parameters from the assigned distributions for a cohort moving through the model. The output of the probabilistic sensitivity analysis is 1,000 ICERs, which can be interpreted as the range of potential outcomes that could be expected given the range of input parameters assumed.[102]

The resulting ICERs are plotted on the x-y axis and interpreted as described above. Multiple ICERs allow for the calculation of the percentage of ICERs falling in each quadrant. If all ICERs fall in a single quadrant, then it can be said with some certainty that the true value lies in that quadrant, provided the model is comprehensive and correctly constructed. It is more likely that the ICERs fall in multiple quadrants, or that they fall in the northeast or southwest quadrants, where the determination of the superior treatment depends on how much the payer, in this case, Medicare, is willing to pay per QALY gained.

Results from the probabilistic sensitivity analysis results also were used to plot a cost-effectiveness acceptability curve (CEAC). The CEAC shows the probability that one intervention is more cost-effective than its comparator over a range of WTP value per QALY thresholds.[102] For a given WTP value, the CEAC indicates the probability that implementing the intervention would be the "right" choice, that is, that the cost per QALY gained would be equal to or below the WTP per QALY gained. The inverse of this probability is the likelihood that the intervention would be the wrong choice.[102] Plotting the CEAC requires the calculation of the incremental net benefit (INB) for each iteration of the Monte Carlo simulation, where the INB is defined as:

$$INB = \lambda*(Benefit_{(adjuvant)} – Benefit_{(wait\ and\ see)}) - (Cost_{(adjuvant)} – Cost_{(wait\ and\ see)})$$

and λ is the societal WTP for a QALY.[157] If the INB is positive, the ART approach offers a greater net benefit. If the INB is negative, the wait and see approach offers a greater net benefit. For a range of λ values, the CEAC represents the proportion of iterations in which the INB is positive.[100]

In scenario analyses, cohort characteristics were changed to evaluate outcomes for men with different disease characteristics than those men represented by the base-case (Figure 13). To reflect the findings presented in Chapter 4 that men do not receive consistent follow-up surveillance over time, the probability of receiving SRT upon

disease recurrence following radical prostatectomy was assumed to be 0.75 for recurrences in the first two years following surgery, 0.50 for recurrences in years 3-4, and 0.25 thereafter. In an additional scenario to evaluate the effect of increasing PSA values over time since radical prostatectomy, PSA level at initiation of SRT was 0.5 ng/ml for recurrences in the first two years following surgery, 1 ng/ml in years 3-4, and 1.5 ng/ml in year 5 and beyond. Scenario analyses also evaluated outcomes for four groups: men with and without positive surgical margins and with and without seminal vesicle invasion.

Figure 13. Scenarios Evaluated in Scenario Analyses

- Time-varying probability of SRT receipt following recurrence
- SRT initiated at different PSA levels:
  - 0.1 ng/ml
  - 0.5 ng/ml
  - 0.75 ng/ml
  - 1.5 ng/ml
  - 3.0 ng/ml
- Time-varying PSA level at SRT initiation
- Positive surgical margins
- Negative Surgical margins
- Seminal vesicle invasion
- No seminal vesicle invasion

Note: PSA: prostate-specific antigen; SRT: salvage radiation therapy

All analyses were conducted in TreeAge Pro 2011 (Williamstown, MA) and followed the guidelines set forth by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Modeling Good Research Practices Task Force.[169] This research was approved by the Public Health and Nursing Institutional Review Board of the University of North Carolina at Chapel Hill.

6.3. Results

6.3.1. Base-case Scenario

In the base-case scenario, treating all men with adjuvant radiation following radical prostatectomy resulted in a cost of $31,021 with a benefit of 10.45 QALYs per person (Table 20). In comparison, waiting until PSA recurrence to initiate SRT would be expected to result in $12,726 lower cost and increase quality-adjusted survival by 6 months. That is, the wait and see approach to radiation is both less costly and results in better outcomes in terms of QALYs (i.e., the wait and see approach dominates ART). Although the wait and see approach results in

more instances of recurrence overall (79.4% of men experience disease recurrence in the wait and see arm compared to 61.9% of men in the ART arm), fewer men develop metastatic disease or die from prostate cancer. Under the wait and see approach, 32.4% of men are expected to develop metastatic disease, and 19.1% of men will die from prostate cancer. Treating all men with adjuvant radiation results in 36.7% of the cohort developing metastatic disease and 22.7% of men dying from prostate cancer. All of the men treated with the ART approach received radiation therapy, compared to 59.1% of the men treated with the wait and see approach.

Table 20. Base-case Results for Adjuvant Radiation Therapy versus the Wait and See Approach to Radiation Therapy

	Adjuvant	Wait and See
Cost (in 2011$)	$31,021	$18,295
Effect (QALYs)	10.45	10.95
% Experiencing recurrence	61.9	79.4
% Experiencing metastatic disease	36.7	32.4
% of Deaths due to prostate cancer	22.7	19.1
% Receiving SRT		59.1

Note: CI: confidence interval; QALY: quality-adjusted life-year; SRT: salvage radiation therapy

6.3.2. One-way Sensitivity Analysis

All model outcomes were calculated using both the high and low values for all model inputs listed in Table 18. For all one-way sensitivity analyses, the cost associated with ART was greater than the cost associated with the wait and see approach. One extreme input value resulted in an ICER in which ART was not dominated by the wait and see approach. When the proportion of men who receive SRT after recurrence was set to zero, the ICER was $41,762 per QALY. Using a WTP per QALY value of $50,000, the difference in INB between the high and low parameter values was greatest for the proportion of men who receive SRT after recurrence ($55,123), followed by the probability of progression-free survival following ART ($36,789), the probability of

progression-free survival following SRT ($32,048), and the probability of progression-free survival following radical prostatectomy ($25,397).

In order to further investigate the sensitivity of results to the proportion of men receiving SRT after recurrence, outcomes were calculated for a range of proportion values (Table 21). For all possible values of the proportion of men receiving SRT after recurrence, ART is always the more costly alternative and the wait and see approach always results in more instances of disease recurrence. The two alternatives are equivalent in terms of QALYs when 36% of men experiencing recurrence receive SRT, and ART becomes cost-effective when 6.9% of men experiencing recurrence receive SRT (using a $50,000 per QALY WTP threshold). ART and the wait and see approach are equivalent in terms of the proportion of men developing metastatic disease and the proportion of deaths due to prostate cancer when approximately 55% of men with recurrence receive SRT.

6.3.3. Probabilistic Sensitivity Analysis

In the probabilistic sensitivity analysis, 75% of men experiencing recurrence were assumed to receive SRT. All other parameters values were drawn from their associated distributions. Across 1,000 iterations, the average cost associated with the wait and see approach was $17,779, compared to $30,927 under the ART approach (Table 22). The wait and see approach resulted in 0.51 more QALYs on average, associated with a quality-adjusted survival difference of 186 days. As in the base-case, more individuals experienced disease recurrence with the wait and see approach (77.3% compared to 59.4%), but the wait and see approach was associated with a lower proportion of men developing metastatic disease (31.2% compared to 35.3%) and a lower proportion of men dying of prostate cancer (18.4% compared to 21.9%).

Table 21. Results by Proportion of Men Experiencing Biochemical Recurrence who Receive Salvage Radiation Therapy

	ART	0% SRT	25% SRT	50% SRT	75% SRT	100% SRT
Cost (in 2011$)	$31,021	$11,773	$13,947	$16,121	$18,295	$20,470
Effect	10.45	9.99	10.31	10.63	10.95	11.27
ICER (compared to ART)	--	$41,762	$120,412	Dominated	Dominated	Dominated
% Experiencing recurrence	61.9	79.4	79.4	79.4	79.4	79.4
% Experiencing metastatic disease	36.7	48.9	43.4	39.4	32.4	26.9
% of Deaths due to prostate cancer	22.7	31.3	27.2	23.2	19.1	15.0
% Recurring and receiving SRT		0	19.1	37.9	59.1	78.8

*ICER = incremental cost-effectiveness ratio (in 2011$/QALY gained) of ART compared to SRT, **Dominated—SRT dominates ART (i.e., SRT costs less and results in better outcomes as measured in QALYs gained compared to ART)

Note: SRT: salvage radiation therapy; ART: adjuvant radiation therapy; QALY: quality-adjusted life year

Table 22. Probabilistic Sensitivity Analysis Results

	Adjuvant		Wait and See	
	Estimate	95% CI	Estimate	95% CI
Cost (in 2011$)	$30,927	23,122-41,226	$17,779	9,277-25,718
Effect (QALYs)	10.45	8.83-12.20	10.96	9.79-12.24
% Experiencing recurrence	59.4	24.4-90.6	77.3	47.8-95.6
% Experiencing metastatic disease	35.3	12.9-55.4	31.2	17.2-44.8
% of Deaths due to prostate cancer	21.9	7.2-41.5	18.4	9.3-35.1
% Receiving SRT			57.5	35.4-71.3

Note: CI: confidence interval; QALY: quality-adjusted life-year; SRT: salvage radiation therapy

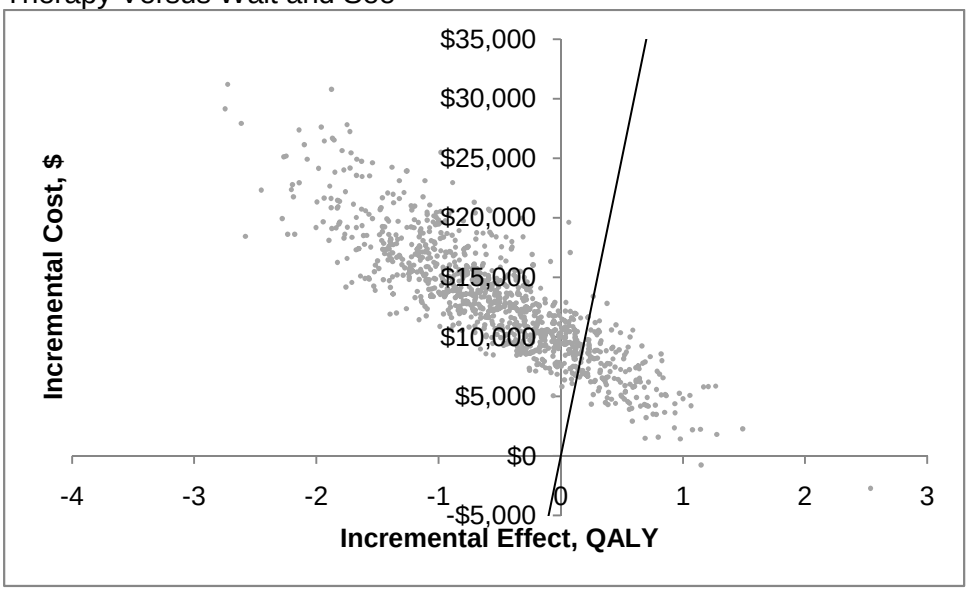
The range of ICERs, when plotted on the ICER plane, spread across the northwest and northeast quadrants (Figure 14). Using a WTP per QALY threshold of $50,000, the wait and see is more cost-effective than the ART approach 84.3% of the time. That is, the point estimates from 84.3% of the 1,000 iterations fall to the left of the threshold line as depicted in Figure 13. In all but 2 model iterations, ART was more expensive than wait and see. In 75.6% of the iterations, ART was also less effective in terms of QALYs. These iterations are represented by the points in the northwest quadrant of the ICER plane in Figure 14. This means that no matter how much society was willing to pay for an additional QALY, the wait and see approach would result in the greatest net benefit 75.6% of the time. In 8.7% of the iterations the ICER fell to the left of the vertical axis, indicating that ART was more effective, but right of the WTP threshold, indicating that the cost per QALY gained was higher than society's WTP.

6.3.4. Scenario Analyses

In the base-case and probabilistic sensitivity analysis presented above, the proportion of men receiving salvage radiation therapy in response to disease recurrence remained constant over time at 75%. This proportion is likely not constant over time, as initiation of salvage radiation is dependent on detection of PSA recurrence through PSA

surveillance, which, as shown in Chapter 4, declines over time. In a scenario analysis, the probability of receiving SRT upon disease recurrence following radical prostatectomy was assumed to be 0.75 for recurrences in the first two years following surgery, 0.50 for recurrences in years 3-4, and 0.25 thereafter. All other model parameters were drawn from their associated distributions, and 1,000 model iterations were run.

Figure 14. Incremental Cost-effectiveness Ratio Plane Comparing Adjuvant Radiation Therapy Versus Wait and See



*Each point represents the incremental cost and incremental effect of adjuvant radiation therapy compared to the wait and see approach for a single iteration of the model. The x-axis is quality-adjusted life years and the y-axis is cost in 2011 US$. All points in the northwest quadrant of the graph represent model iterations in which adjuvant radiation therapy was more expensive and less effective than the wait and see approach (75.6%). The diagonal line represents a willingness to pay threshold of $50,000 per QALY. All points to the right of the threshold represent model iterations in which adjuvant radiation therapy was cost-effective compared to a wait and see approach (15.7% of points). The remaining 8.7% of points that fall between the y-axis and the threshold represent model iterations in which adjuvant radiation therapy was more costly and more effective than the wait and see approach but the cost per QALY gained was greater than $50,000.

Note: QALY: quality-adjusted life year. Willingness to pay threshold of $50,000 per quality-adjusted life-year

When the proportion of men who receive SRT following disease recurrence decreases over time, the wait and see approach remains superior to ART. Using a WTP threshold of $50,000 per QALY, the wait and see approach was the more cost-effective

option in 74.5% of model iterations. Compared to a scenario in which 75% of men with recurrence receive SRT no matter when recurrence is experienced, the time-varying SRT rate is associated with more men developing metastatic disease (37.3% when the SRT rate varies over time versus 31.2% when 75% of recurrences receive SRT) and more deaths due to prostate cancer (22.4% when the SRT rate varies over time versus 18.5% when 75% of recurrences receive SRT).

I also modeled four cohorts of men who received SRT at different PSA levels. In the Southwest Oncology Group (SWOG) clinical trial, among the 65 patients in the wait and see group received radiation therapy with known treatment initiation dates, 45.1% initiated radiation therapy after PSA relapse and objective recurrence (for example, biopsy-proven local recurrence).[8] Among these men, the median PSA level at the time of initiation of SRT was 0.75 ng/ml,[9] compared to the 0.50 ng/ml used in the base-case analysis. Four additional cohorts of men were created based on PSA level at SRT initiation and faced a different probability of progression following SRT. Each probability was drawn from its associated distribution (Table 23). Separate probabilistic sensitivity analyses were conducted for cohorts of men that initiated SRT at PSA level of 0.1 ng/ml, 0.75 ng/ml, 1.5 ng/ml, and 3 ng/ml. Base-case results are presented in Table 24.

Table 23. Probabilities Associated with Disease Recurrence Following Salvage Radiation Therapy, by PSA Level at Initiation

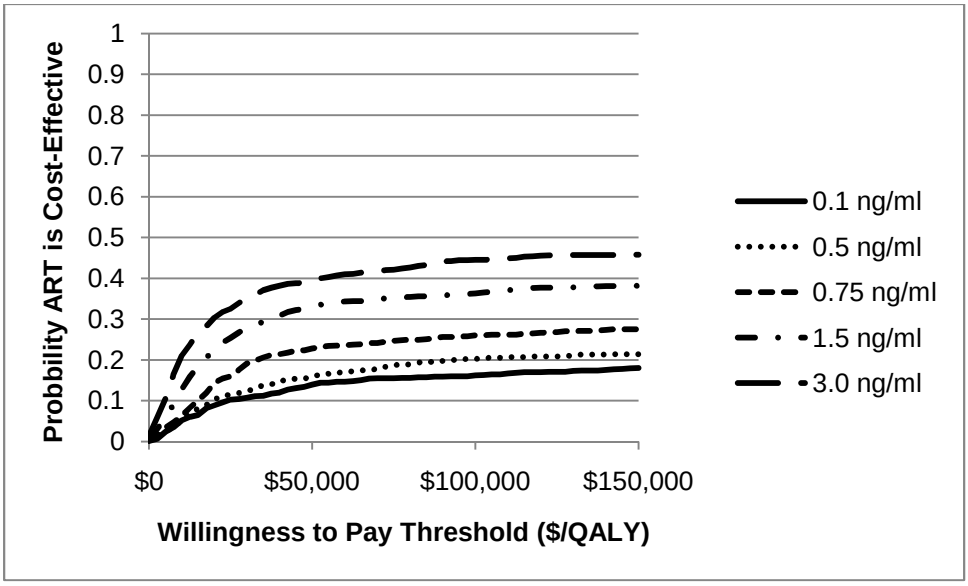
Probabilities	Base-case value	SD	Lower 95% CI	Upper 95% CI
Progression following SRT*[5]				
PSA = 0.1 ng/ml	0.37	0.07	0.225	0.515
PSA = 0.5 ng/ml	0.45	0.11	0.234	0.667
PSA = 0.75 ng/ml	0.50	0.20	0.108	0.892
PSA = 1.5 ng/ml	0.65	0.13	0.395	0.905
PSA = 3 ng/ml	0.80	0.16	0.486	0.999

*Time period for all probabilities is 6 years, beta distributions used for all probabilities.

Note: PSA: prostate-specific antigen; SD: standard deviation; CI: confidence interval; SRT: salvage radiation therapy; ng/ml: nanograms/milliliter

When SRT is initiated at 0.1 ng/ml, the wait and see approach dominates ART in 13.9% of iterations (assuming a WTP per QALY of $50,000). When SRT is initiated at 3 ng/ml, ART is the more cost-effective approach in 40% of iterations. Figure 15 presents the CEACs associated with ART for each of the 5 cohorts of men. For all WTP thresholds over the range $0 to $150,000 per QALY, the ART approach is cost-effective less than half of the time. There is a greater probability that the wait and see approach will be cost-effective, regardless of the PSA level at SRT initiation. The probability that ART is cost-effective compared to the wait and see approach is lowest for men who initiate SRT at low PSA levels and highest for men who initiate SRT at higher PSA levels.

Figure 15. Cost-effectiveness Acceptability Curves, by PSA Level at SRT Initiation



*Each curve represents the probability that ART will be cost-effective compared to the wait and see approach to radiation therapy over a range of willingness to pay values. The willingness to pay values represent the maximum value society is willing to pay for an additional quality-adjusted life year. The threshold values are shown on the x-axis and the probability that ART is cost-effective is shown on the y-axis. Each curve represents the relationship between the willingness to pay threshold and the probability for a different PSA value at initiation of SRT. The curve associated with a PSA level of 0.5 ng/ml at SRT initiation represents the base-case.

Note: PSA: prostate-specific antigen, ART: adjuvant radiation therapy, QALY: quality-adjusted life year; SRT: salvage radiation therapy

Table 24. Results by PSA Level at Initiation of Salvage Radiation Therapy

	ART	SRT at 0.1 ng/ml	SRT at 0.5 ng/ml	SRT at 0.75 ng/ml	SRT at 1.5 ng/ml	SRT at 3 ng/ml
Cost	$31,021	$17,703	$18,295	$18,645	$19,617	$20,520
Effect	10.45	11.06	10.95	10.88	10.70	10.51
ICER (compared to ART)	--	Dominated**	Dominated	Dominated	Dominated	Dominated
% Experiencing recurrence	61.9	79.4	79.4	79.4	79.4	79.4
% Experiencing metastatic disease	36.7	29.7	32.4	33.9	37.9	41.2
% of Deaths due to prostate cancer	22.7	17.4	19.1	20.0	22.6	25.0
% Recurring and receiving SRT		59.1	59.1	59.1	59.1	59.1

*ICER = incremental cost-effectiveness ratio (in 2011$/QALY gained) of ART compared to SRT. **Dominated—SRT dominates ART (i.e., SRT costs less and results in better outcomes as measured in QALYs gained than ART)

Note: SRT: salvage radiation therapy; ART: adjuvant radiation therapy; PSA: prostate-specific antigen

Table 25. Results by Tumor Characteristics

	Positive SM		Negative SM	
	ART	WS	ART	WS
Cost (in 2011$)	$30,303	$18,861	$30,805	$14,883
Effect	10.60	10.89	10.50	11.20
ICER	Dominated		Dominated	
% Experiencing recurrence	57.7	81.1	60.7	65.8
% Experiencing metastatic disease	33.9	33.4	35.8	28.1
% of Deaths due to prostate cancer	20.8	19.8	22.1	16.2
% Recurring and receiving SRT		60.3		48.9

	SV Invasion		No SV Invasion	
	ART	WS	ART	WS
Cost (in 2011$)	$34,896	$20,886	$27,367	$15,586
Effect	9.63	10.65	11.17	11.21
ICER	Dominated		Dominated	
% Experiencing recurrence	80.4	85.2	38.5	70.7
% Experiencing metastatic disease	50.4	38.1	21.7	27.6
% of Deaths due to prostate cancer	32.6	22.9	13.0	15.9
% Recurring and receiving SRT		63.5		52.6

*ICER = incremental cost-effectiveness ratio (in 2011$/QALY gained) of ART compared to SRT. **Dominated - SRT dominates ART (i.e., SRT costs less and results in better outcomes as measured in QALYs gained than ART)

Note: SRT: salvage radiation therapy; ART: adjuvant radiation therapy; SM: surgical margins; SV: seminal vesicle

If, as has been suggested by the research presented in Chapter 4, men receive less intensive PSA surveillance as time from surgery increases, it is possible that the average PSA at SRT initiation increases as well. PSA level at initiation of SRT was 0.5 ng/ml for recurrences in the first two years following surgery, 1 ng/ml in years 3-4, and 1.5 ng/ml in year 5 and beyond. This led to the creation of a scenario in which 75% of PSA recurrences within the first two years after surgery are treated with SRT at a PSA level of 0.5 ng/ml, 50% of PSA recurrences in years 3 and 4 were treated with SRT at a PSA level of 1 ng/ml, and 25% of PSA recurrences in year 5 and beyond were treated with SRT at a PSA level of 3 ng/ml.

In a probabilistic sensitivity analysis of a scenario in which rates of SRT receipt and PSA levels at SRT initiation varied over time, average cost of the wait and see approach was $16,299 (compared to $30,598 for ART) and the wait and see approach only resulted in an increase of approximately 4 days of quality-adjusted survival compared to ART. Compared to ART, the wait and see approach resulted in an increase in the proportion of men developing metastatic disease (41.8% versus 35.2%) and dying of prostate cancer (25.4% versus 21.9%). With a WTP threshold of $50,000 per QALY, ART was cost-effective in 36.7% of model iterations.

For the cohort of individuals without seminal vesicle invasion, the adjuvant approach to radiation therapy results in higher costs and lower QALYs compared to the wait and see approach (Table 25). The wait and see approach is associated with more cases of recurrence, more cases of metastatic disease, and more deaths due to prostate cancer. The outcome in terms of costs and QALYs is the same in the cohort of individuals with seminal vesicle invasion, but for these individuals the wait and see approach is associated with higher recurrence rates but fewer cases of metastatic disease and fewer prostate cancer deaths. At a WTP threshold of $50,000 per QALY, the ART approach is cost-effective 19% of the time for individuals without seminal

vesicle invasion, compared to less than 1% of the time for individuals with seminal vesicle invasion.

Regardless of surgical margin status, ART results in higher costs and lower QALYs than using the wait and see approach to radiation therapy. For the cohorts of men with positive and negative surgical margins, ART is associated with a lower recurrence rate but a higher rate of metastatic disease and higher proportion of prostate cancer deaths. For individuals with negative surgical margins, ART is the more cost-effective option 2% of the time (using a WTP threshold of $50,000 per QALY). For individuals with positive surgical margins, ART is the more cost-effective option 8% of the time.

6.4. Discussion

Overall, the wait and see approach to radiation therapy resulted in lower costs and better quality-adjusted life expectancy than ART. Whereas cost was always higher under the adjuvant radiation approach, the preferred alternative determined by other outcomes was sensitive to the proportion of men experiencing disease recurrence following radical prostatectomy who received SRT and PSA level at time of salvage therapy initiation.

The true proportion of men who receive SRT after disease recurrence is unknown, and likely would vary by patient characteristics, surveillance intensity, and local practice patterns. In the SWOG study, 111 men in the wait and see group experienced recurrence or died during the study period. Of these 111 men, 70 received radiation therapy (63%).[8] The actual proportion of men receiving SRT could have been higher, depending on when deaths in this group occurred. However, of these 70 men many did not initiate radiation therapy until an objective recurrence as defined by biopsy-detected local disease (which is more advanced than a recurrence detectable only by rising PSA levels). The probabilities associated with the risk of recurrence following SRT

assume that SRT is initiated upon PSA-only recurrence and that radiation therapy is administered before objective recurrence. By this definition, only 55.4% of the sample in the SWOG trial would have been considered to have received SRT.[8] Based on the patterns observed in the SWOG study, the 75% salvage administration rate used in this model may be on the upper end of the range of plausible values.

The results from this model do not reflect the improved metastases-free survival associated with ART observed in the SWOG study. One reason for this difference is the probability of SRT initiation, as discussed above. Additionally, the entire cohort of men modeled was assumed to achieved an undetectable PSA level after prostatectomy, compared to 66% of men in the SWOG study.[8] The presence of elevated PSA following surgery is associated with shorter disease-free time following salvage radiation,[5] so the results observed in the SWOG study are likely not applicable to a cohort of men with undetectable PSA following surgery (< 0.1 ng/ml). Additionally, the men in the SWOG study, as clinical trial participants, may not be representative of the Medicare population, which limits the generalizability of trial results.[14]

The results by tumor characteristics suggested that men with positive surgical margins and seminal vesicle invasion may benefit from the wait and see approach to radiation therapy. Although in all scenarios adjuvant radiation was associated with a lower proportion of men who experienced biochemical recurrence, men who experienced biochemical recurrence after ART were more likely to go on to experience metastatic disease. This observation is in contrast to men who experienced biochemical recurrence after radical prostatectomy and received SRT, which essentially bought them additional time until progression to metastatic disease. These results should be interpreted with caution, however, as they are based on progression probabilities observed in an unplanned subgroup analysis from the ARO trial and sample sizes are relatively small.[6]

As shown by the change in results when considering SRT administered at a PSA level of 0.1 ng/ml compared to 3 ng/ml, the model is sensitive to changes in the probability of progression following SRT. SRT was most effective when initiated in all patients with a biochemical recurrence following radical prostatectomy and at lower PSA levels. No published clinical trials evaluate the ideal timing of SRT initiation, but research suggests that a PSA increase from an undetectable level to 0.1 ng/ml may be large enough to consider SRT initiation.[81] Initiating SRT this early greatly affects the probability of progression following SRT and swings the results from this model even more in favor of the wait and see approach.

As with all simulation models, the results are only as valid as the model construction and input values. This model was constructed based on previous models of prostate cancer progression[112,118] and with input from specialists in urology and oncology. When at all possible, input values were representative of the population of men for whom ART would be appropriate. This approach was not possible in all cases, particularly with regards to utility values and probabilities associated with progression from biochemical recurrence to metastatic disease. That is, these input values came from studies where the sample was not restricted to men with intermediate- or high-risk disease. Men who are initially diagnosed with low-risk disease may have lower progression-related probabilities, which may mean that the probabilities used in this model are biased in the downward direction. The results from this model are roughly similar to those reported in previous decision analyses related to radiation therapy in prostate cancer although it is not appropriate to directly compare the results due to differences in model construction, patient population, and outcomes of interest.[118,170]

Of the three clinical trials to compare ART to a wait and see approach, only one trial has demonstrated improved metastases-free and overall survival associated with ART.[9] The results from this model suggest, however, that although the ART approach

reduces the proportion of men who experience disease recurrence, the wait and see approach may be more effective in reducing the proportion of men who develop metastatic disease and the proportion of men who die from prostate cancer. Essentially, SRT increases the time from initial recurrence to progression to metastatic disease, which creates a survival advantage associated with this approach. The success of the wait and see approach in terms of quality-adjusted life expectancy, metastases, and prostate cancer deaths depends in part upon two factors that are unknown at the time of surgery: the proportion of men experiencing biochemical recurrence who receive SRT and PSA level at SRT initiation.

Post-operative surveillance through frequent PSA testing can increase the likelihood of detecting rising PSA levels and help inform the decision to initiate SRT. This surveillance is essential if the benefits associated with the wait and see approach compared to ART are to be realized. The analysis in Chapter 4 suggests that PSA surveillance decreases over time and that minority groups have lower odds of receiving a PSA test in any given year past radical prostatectomy compared to non-Hispanic Whites. All men, and especially racial minorities, are therefore at increased risk for undetected biochemical recurrence as time from surgery increases. Potential future educational interventions could target both patients and providers and emphasize the importance of developing and following survivorship care plans to increase the probability of detecting disease recurrence through PSA testing as early as possible. Without timely detection of recurrence, men may receive greater benefit from ART following radical prostatectomy; thus, a commitment to a long-term surveillance plan on the part of both patient and provider should be established upon receipt of initial treatment for men eligible for the wait and see approach to radiation therapy.

7. SUMMARY OF FINDINGS, LIMITATIONS, AND FUTURE DIRECTIONS

This study used population-based Surveillance, Epidemiology, and End Results (SEER)-Medicare data, published clinical trial results, and peer-reviewed literature to examine patterns of prostate-specific antigen (PSA) surveillance and the implications surveillance patterns may have on the decision to implement radiation therapy adjuvant to radical prostatectomy or to delay radiation therapy until there is evidence of disease recurrence. This study represents one of the first attempts to directly link PSA surveillance and secondary treatment decisions.

7.1. Summary of Findings

In Chapter 4, I examined the effect of individual-, tumor-, and community-level factors on the likelihood of receiving PSA tests in accordance with National Comprehensive Cancer Network (NCCN) Guideline recommendations for prostate cancer patients age 65 and older who receive radical prostatectomy for intermediate- and high-risk disease. Overall, receipt of PSA testing following treatment was high, with 96% of men receiving at least one test the first year after treatment and 80% of men receiving at least one test in the fifth year after treatment. Non-married men, men with less advanced disease, and non-Hispanic Blacks and Hispanics had lower odds of test receipt, but the odds associated with these characteristics were much lower than the odds associated with time elapsed since treatment. None of the community-level factors had a significant effect on the odds of receiving at least one test in a 1-year period, but four of the five factors (Medicare health maintenance organization (HMO) penetration, population density, social capital, and racial/ethnic isolation/segregation) had a significant influence on the odds of receiving a test in a 6-month period.

The finding of a racial disparity between non-Hispanic Whites and other groups is in accord with previously reported racial differences in prostate cancer treatment and mortality,[68,69] and the difference in test receipt between non-Hispanic Blacks and non-Hispanic Whites is in line with the results reported in the only other study to focus on post-treatment PSA receipt.[70] Although the racial disparity results in no way suggest that differences in surveillance lead to differences in mortality, they do suggest that the difference in surveillance by race may be clinically significant in addition to statistically significant.

The community-level factors were included in the model to measure access to care and social support. The high rate of annual test receipt, combined with the finding of no significant effect of the community-level variables on annual test receipt suggests that most men do not have difficulty getting an annual PSA test. Access to care and social support play a larger role in influencing test receipt in a 6-month period, as semi-annual testing may require more motivation and resources. However, the magnitude of the odds ratios associated with the race/ethnicity and community variables compared to the odds ratios associated with the variables measuring time elapsed since treatment suggest that decreasing disparities related to individual or community characteristics may not be the most efficient strategy to increase overall long-term surveillance. One way to improve test receipt may be to focus on creating educational interventions underscoring the rationale for follow-up strategies that span many years following treatment and to highlight the significance of long-term follow-up as part of a survivorship care plan. These educational interventions should target primary care providers as well as cancer care providers, as the former may play a larger role in delivering follow-up care as time from treatment increases.[47]

Chapter 5 was designed in acknowledgement of changing treatment documentation practices in SEER data and increasing interest in using SEER data to

measure receipt of radiation therapy adjuvant to radical prostatectomy. This study compared SEER treatment data to Medicare claims to determine whether there are biases related to the use of SEER data alone rather than the linked SEER-Medicare data to study adjuvant radiation therapy (ART). Only a small percentage of men overall receive ART (9.7% in SEER, 10.9% in Medicare). Agreement across the two sources was high (94.8%) and was found to vary by registry area and disease severity. However, almost all men with documentation of ART receipt in SEER had Medicare claims for radiation therapy at some point after surgery.

In this study, I observed limited bias caused by using SEER data only to study ART rather than validating radiation receipt using Medicare claims, particularly for men with poorly-differentiated tumors. However, only a small number of cases are affected by disagreement, implying that it is reasonable to use SEER data alone to examine ART. The low rates of ART among the SEER population reported by previous studies[86,87] are likely the result of limited adoption of ART as a treatment modality rather than any underreporting of ART in SEER data.

Chapter 6 tied together the issues of PSA surveillance and ART through a cost-utility model. I used a Markov cohort model to compare two approaches to radiation therapy following radical prostatectomy: ART versus a wait and see approach in which salvage radiation therapy (SRT) is initiated only upon evidence of disease recurrence (marked by increasing PSA values). Treating all qualifying men with ART following radical prostatectomy resulted in an expected cost of $31,021 with a benefit of 10.45 quality-adjusted life-years (QALYs). Waiting until PSA recurrence to initiate SRT resulted in an expected cost of $18,295 with a benefit of 10.95 QALYs. That is, the ART approach was more expensive and resulted in slightly worse outcomes in terms of QALYs. Although more men developed disease recurrence under the wait and see approach, it was associated with lower rates of metastatic disease and death from

prostate cancer. These results assume that 75% of men who experience disease recurrence in the form of increasing PSA values receive SRT. If this proportion falls to 36% of men, the two strategies are equivalent in terms of QALYs, but the wait and see approach is still the more cost-effective option as it remains less costly. The ART approach becomes cost-effective (using a $50,000 per QALY willingness to pay threshold) when only 6.9% of the men experiencing recurrence receive SRT. I used the results of Chapter 4 to inform the creation of several scenarios, which I then used to assign model parameters. Since the results from Chapter 4 indicate that men are less likely to receive surveillance PSA testing over time, I allowed the proportion of men who receive SRT following recurrence to decrease over time (reflecting that recurrence that is not detected through PSA surveillance will not be treated). I also created a scenario in which the PSA value at the time of SRT initiation increased over time, reflecting that less frequent PSA testing may result in higher PSA values at detection of recurrence. For these scenarios, as well as scenarios for men with varying disease characteristics, the wait and see approach was almost always the more cost-effective option although it often resulted in higher rates of metastatic disease and prostate cancer deaths.

The success of the wait and see approach in terms of quality-adjusted life expectancy, metastases, and prostate cancer deaths depends in part upon two factors that are unknown at the time of surgery: the proportion of men experiencing biochemical recurrence who receive SRT and PSA level at SRT initiation. Post-operative surveillance through frequent PSA testing can increase the likelihood of detecting rising PSA levels and help to inform the decision to initiate SRT. The analysis in Chapter 4 suggests that PSA surveillance decreases over time and that minority groups have lower odds of receiving a PSA test in any given year past radical prostatectomy than non-Hispanic Whites. All men, and especially racial minorities, are therefore at increased risk for undetected biochemical recurrence as time from surgery increases. Without timely

detection of recurrence, men may receive greater benefit from ART following radical prostatectomy; thus, a commitment to a long-term surveillance plan on the part of both patient and provider should be established upon receipt of initial treatment for men eligible for the wait and see approach to radiation therapy.

7.2. Limitations

The findings from Chapters 4 and 5 are limited by the use of claims data to identify PSA testing and radiation therapy receipt, as claims provide no information on test or treatment motivation. That is, it is not possible to distinguish between men who are receiving multiple PSA tests to follow-up on previous test results and men who are receiving multiple tests due to lack of communication across providers. Furthermore, the results of the PSA tests are not available in these data, which limits the ability to draw conclusions regarding the frequency of abnormal (in this context, detectable) PSA results and any actions (i.e., initiation of salvage treatment) that might be indicated on the basis of those results. This relates to one limitation of using claims to examine radiation therapy, as it is impossible to know whether radiation therapy delivered within 180 days of radical prostatectomy was initiated in response to rising PSA levels following surgery or was delivered as part of an initial treatment plan.

Additionally, the limitation of the sample to men with Medicare fee-for-service insurance means that results may not be generalizable to the entire prostate cancer population or to the entire Medicare population. Results are also only applicable to the portion of prostate cancer patients and survivors who receive radical prostatectomy soon after diagnosis. As more than 80% of the men in SEER-Medicare with qualifying disease characteristics did not meet the surgical inclusion criteria for these studies, the group of men to whom these results can be generalized is relatively small. Findings of this research may not apply to younger men who are not covered by Medicare as these men

may face a different set of competing health risks and experience different treatment patterns.[16,18]

As with all simulation models, the results presented in Chapter 6 are only as valid as the model construction and input values. This model was constructed based on previous models of prostate cancer progression[112,118] and with input from specialists in urology and oncology. When at all possible, input values were representative of the population of men for whom ART would be appropriate. There has been one clinical trial that has reported on metastasis-free and overall survival associated with ART compared to a wait and see approach to radiation therapy,[9] but differences in the clinical trial inclusion criteria and the characteristics of the hypothetical model cohort make it impossible to make meaningful comparisons between trial results and the model output.

7.3. Future Directions

I believe that the analyses presented in Chapters 4 and 6 offer the most interesting and fruitful extensions for future research. A natural extension of the research in Chapter 4 would be to evaluate the validity of using PSA claims as a marker of post-prostatectomy surveillance. There are currently no studies validating the use of PSA claims in the Medicare data. The use of PSA tests as a marker of quality surveillance is predicated upon the assumption that men who receive intense PSA surveillance would be more likely to initiate secondary therapy than men who do not receive PSA tests. If, however, a significant proportion of men receive some form of secondary therapy without claims for PSA tests, then PSA claims may not be an indicator of post-prostatectomy surveillance intensity or quality. The sample for this subgroup analysis would be similar to the Chapter 4 sample but would include only those men who received either salvage radiation therapy or hormonal therapy at least six months after prostatectomy. If the number of men with claims for secondary therapy and no PSA surveillance is high, practice patterns in some areas, regions, or among some urologists

may indicate the use of secondary therapy without evidence of a rising PSA. I do not, however, expect this to be the case as this would assume practice patterns that are not guideline-appropriate and do not make use of an easily obtained and highly sensitive and specific tumor marker.[171] If, however, there are a large number of men with secondary treatment and no surveillance PSA claims, future research is warranted.

To the extent that an abnormal result in this context (any detectable PSA greater than 0.1 ng/ml) may not be flagged as "abnormal" on standard laboratory result reports (which typically set a threshold of 2.5 or 4.0 ng/ml), the possibility of missed opportunities for potentially curative early salvage treatment certainly exists. Future studies to evaluate the extent of this potential phenomenon are warranted, given evidence supporting optimal efficacy for salvage radiation when delivered at low PSA levels, with progressively poorer results for patients receiving salvage treatment at progressively higher PSA levels, all below the standard screening-context "normal" ranges of PSA.[5]

Although PSA values are more directly interpretable following radical prostatectomy than other initial therapies, I could expand the sample from the Chapter 4 analysis to include men who receive radiation or hormonal therapy as an initial treatment. The single other study of PSA surveillance testing found that there were differences in test receipt by type of initial treatment.[70] If men who receive other types of treatment do not receive surveillance at the same high rate as radical prostatectomy patients, there may be some cause for concern that overall follow-up and survivorship care in these other patient groups is lacking.

The frequency of PSA surveillance testing observed in radical prostatectomy patients, along with the suggestion that testing rates are not constant over the course of a year (see Figures 6 and 8 in Chapter 4) may indicate that PSA surveillance would best be measured in a survival-analysis framework. The primary drawback of using the

logistic-based GEE model, in contrast to survival analysis methods designed for recurrent events (such as shared frailty and Andersen-Gill Cox models), is the relatively clumsy manner in which time can be addressed. In the Chapter 4 analysis, I dropped partial periods of data, but continuous time models could make full use of the entire surveillance period. Future work could examine the use of survival analysis to address PSA surveillance.

An alternate modeling strategy also could be used to generate additional results from the Markov model. In contrast to cohort models, individual-level models (often called microsimulations[172]) evaluate outcomes for one person at a time. Individual, rather than cohort, modeling requires more inputs and increases computational burden, but produces more accurate estimates of population-level cost, utility, and event frequency.[173] Additionally, individual-level modeling makes it possible to model the dependence of transition probabilities on multiple risk factors and patient histories that change over time.[174] This allows for the construction of a model that is much more representative of the real world than a cohort model.

The addition of tracker variables, which are global variables that can be associated with each individual within the model to keep a record of the time an individual spends in each state,[175] along with individual-level, rather than cohort modeling would help to make my model more representative of the actual disease course than the straightforward Markov model used in Chapter 6. Individual-level modeling, combined with sensitivity analysis, would combine stochastic uncertainty, parameter uncertainty and patient heterogeneity, all three of which are recommended to account for uncertainty and variability in medical decision models.[172]

For decision-makers, it is not enough to know the probability that a given intervention will be the most cost-effective choice. It is also necessary to know the costs associated with making the wrong choice.[102] The cost of making the wrong decision and

the probability of making the wrong decision jointly determine what is referred to as the expected opportunity loss of the decision or the expected value of perfect information (EVPI).[100] EVPI can be thought of as the maximum value added by further research that would reduce uncertainty in the model parameters.[102] Future research could calculate the EVPI and compare it to the cost of conducting a clinical trial of ART versus a wait and see approach to salvage radiation therapy. If the EVPI is greater than the cost of a trial, then it may be wise to conduct a trial or invest in more research before making treatment recommendations based on model outcomes.

Although the overall EVPI can be informative, it may be much larger than current resources available to conduct further research. In this case, calculating the expected value of perfect information for parameters (EVPPI) can identify the type of future research that would be most useful.[100] In the future, I could use a two-level Monte Carlo simulation method to calculate the EVPPI. This method uses all possible true values for the parameter to calculate opportunity loss and then averages the opportunity loss across all possible parameter values.[157] The EVPPI can be calculated for individual parameters or groups of parameters, with the latter method preferred as a starting point.[100] Creating groups of related parameters and calculating the EVPPI for the set makes sense intuitively, as individual parameters may not be independent, and further research on one parameter may yield information on another parameter.

7.4. Conclusions

Chapters 4 and 6 particularly call attention to the role of PSA surveillance in prostate cancer survivorship care. PSA surveillance is not only essential in the detection of disease recurrence, it is one of the most important factors that influences the success of SRT in response to recurrence. PSA surveillance, though high overall, especially in comparison to surveillance in other cancer survivors, declines over time and is lower in some populations of men. Low rates of PSA surveillance can lead to the missed

opportunity to detect disease recurrence and to initiate SRT when it has the greatest potential to be curative. The most important take-away point from this dissertation research is that a long-term plan for disease surveillance is essential for prostate cancer patients, particularly those who receive radical prostatectomy as initial therapy. This research sets the stage for future educational interventions to target patients and providers and convey the importance of survivorship care in prostate cancer.

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