

PROSTATE CANCER CLINICAL PRACTICE GUIDELINES:
CLINICAL AND ECONOMIC OUTCOMES

By

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This dissertation is dedicated to my grandparents, Lonnie Friday Persons and James Monroe Persons; and Margaret Miller Taylor and Lawrence Dennis Taylor.

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Prostate cancer has a significant impact on public health in the United States.

Despite the high prevalence of prostate cancer, there is still no clear evidence that any one treatment is superior to all others. Furthermore, little is known about the cost of most prostate cancer treatment strategies beyond a 1-year time frame.

We conducted a retrospective cohort study using the Surveillance, Epidemiology, and End Results (SEER)-Medicare database to examine the clinical and economic outcomes of prostate cancer treatment strategies over a 5-year time frame for patients at low and intermediate risk of prostate cancer recurrence. Clinical effectiveness of each treatment strategy was evaluated in terms of prostate cancer-specific survival. Kaplan-Meier survival analysis was used to estimate the survival function and the Cox proportional hazards model was used to test for differences. A modification of Kaplan-Meier survival using inverse probability weighting was used to estimate costs in the presence of censoring.

The study is subject to selection bias because of the lack of randomization. As a result of the selection bias, differences in study end-points may be due to differences in the comparison groups rather than differences in the treatments. However, the use of multivariate analyses allowed us to control for baseline differences in patient characteristics.

We identified statistically significant differences in 5-year prostate cancer-specific cost of healthcare between treatment strategies recommended in prostate cancer practice guidelines, ranging from \$630 (comparing external beam radiotherapy to brachytherapy) and \$6740 (comparing external beam radiotherapy with brachytherapy to expectant management). We also found significant differences in prostate cancer-specific mortality when comparing external beam radiotherapy to expectant management, prostatectomy to expectant management, and prostatectomy to external beam radiotherapy. Finally, we were able to provide valuable information regarding the cost of preventing one death due to prostate cancer over a 5-year time period associated with the use of external beam radiotherapy rather than expectant management (\$600,000), prostatectomy rather than expectant management (\$646,670), and prostatectomy rather than external beam radiotherapy (\$465,710).

CHAPTER 1 INTRODUCTION

Background

Outcomes of health care are typically labeled as one of three types: clinical, humanistic, or economic. Clinical outcomes are results of an intervention or lack thereof expressed in clinical terms. An example of a clinical outcome in the treatment of a post-myocardial infarction patient with a β -blocker would be the prevention of a second myocardial infarction. Humanistic outcomes are typically expressed as the impact of an intervention on an individual's quality of life (QOL); or more specifically, the individual's health related quality of life (HrQOL). An example of a humanistic outcome would be an increase in one of the domains of the patient's SF-36 (a measure of health-related quality of life) score. Economic outcomes are the results of an intervention in monetary terms. Perhaps the simplest method of expressing an economic outcome is to say an intervention results in a net savings of x dollars. However, an economic outcome might also be expressed in terms of the additional cost of an intervention in dollars per unit of clinical improvement.

Need for the Study

Clinical practice guidelines are developed to provide health care practitioners with a guide for treating an illness in a manner most likely to result in the best possible outcomes. The question thus arises, what type of outcomes? All too often, guidelines are developed with a focus on only clinical outcomes. Humanistic and economic outcomes might be considered, but guideline development typically lacks formal consideration of

humanistic and economic outcomes. Originally, guidelines were developed based upon expert opinion, a strategy fraught with potential bias. Today, guidelines are expected to be based on published evidence in peer-reviewed journals identified using systematic searches of the literature (1).

Today, guideline-development groups may consider economic outcomes while formulating recommendations for inclusion in clinical practice guidelines. However, today's consideration of economic outcomes is akin to yesteryear's consideration of clinical evidence; that is, it lacks formal evaluation.

The lack of unlimited health care resources dictates a need for the inclusion of formal cost analyses in the development of clinical practice guidelines that shape much of the practice of medicine in today's society. The Institute of Medicine (2, p. 25) has called for clinical practice guidelines to be "accompanied by explicit projections of the health and *cost outcomes* [emphasis added] expected from the use of particular services or procedures."

In many clinical scenarios, multiple treatment strategies result in equivalent clinical outcomes. Such scenarios dictate a need for some other criterion on which to determine the preferred treatment strategy. Given that health care resources are limited, economic outcomes may be a good criterion for choosing treatment strategies.

Purpose of the Study

Our study used formal economic analysis methods to estimate the *cost outcomes* of interventions proposed by clinical practice guidelines. We applied economic analysis methodologies to the recommendations in the National Comprehensive Cancer Network (NCCN) prostate cancer clinical practice guideline for patients with cancer localized to the prostate.

We chose prostate cancer guidelines for two reasons. First, prostate cancer is a significant public health concern, with 230,855 men expected to have been diagnosed with prostate cancer and 29,089 men expected to have died of prostate cancer in the United States during 2004 (3). Second, the guidelines are not able to recommend one treatment strategy over all others on the basis of clinical evidence for many stages of prostate cancer (4). Rather, the guidelines provide several treatment strategies as being acceptable for many prostate cancer clinical scenarios. Because of scenarios (such as those in the NCCN prostate cancer clinical practice guideline) in which one treatment strategy cannot be advocated above all others on the basis of clinical evidence, consideration of economic and/or humanistic outcomes is essential.

Specific Objectives

In demonstrating the use of formal economic analysis methods to estimate the cost outcomes of interventions included in clinical practice guidelines, our study addressed three specific objectives. First, we determined the clinical effectiveness of each NCCN prostate cancer clinical practice guideline treatment recommendation for patients at low and intermediate risk of prostate cancer recurrence (i.e., patients with cancer localized to the prostate) using observational data. Second, we determined the cost for each treatment option. Finally, we determined the minimum willingness-to-pay value resulting in a treatment that is both more effective and more expensive being cost effective.

Research Questions and Hypotheses

The first research question examined the clinical effectiveness of prostate cancer treatment strategies among men at least 65 years of age when diagnosed with prostate cancer using the SEER-Medicare linked database for the years 1992 to 1999. The

clinical effectiveness of each strategy was defined as the treatment-specific survival function describing the time to death due to prostate cancer.

Research Question 1

Is there a difference in clinical effectiveness between expectant management, 3-dimensional conformal radiotherapy (3D-CRT), prostatectomy, brachytherapy, and 3D-CRT with brachytherapy among newly diagnosed prostate cancer patients at least 65 years of age at low or intermediate risk of prostate cancer recurrence?

Research Question 1 Hypothesis

The null hypothesis was that the expectant management, 3D-CRT, prostatectomy, brachytherapy, and 3D-CRT with brachytherapy survival functions are all equal. The alternative hypothesis was at least one of the survival functions differed.

The second research question examined the cost of prostate cancer treatment strategies among men at least 65 years of age when diagnosed with prostate cancer. Relevant costs included both the cost of the initial treatment and all prostate cancer-specific follow-up costs.

Research Question 2

Is there a difference in prostate cancer-specific health care costs between expectant management, 3D-CRT, prostatectomy, brachytherapy, and 3D-CRT with brachytherapy among newly diagnosed prostate cancer patients at least 65 years of age at low or intermediate risk of prostate cancer recurrence?

Research Question 2 Hypothesis

The null hypothesis was the prostate cancer-specific health care costs for expectant management, 3D-CRT, prostatectomy, brachytherapy, and 3D-CRT with brachytherapy

are all equal. The alternative hypothesis was the cost was different for at least one of the treatment strategies.

Summary

The long-term goal of our study was to demonstrate the use of formal economic analyses in evaluating treatment strategies being considered for inclusion in clinical practice guidelines. It is hoped that such a demonstration will foster guideline development panels to conduct formal economic analyses themselves, or to commission such analyses for use in the guideline development process and thus lead to the advancement of health care interventions based on clinical and economic impact, rather than clinical impact alone. Beyond mere consideration of economic outcomes, it is hoped the results of economic analyses of proposed guideline recommendations will be used to provide a supplemental grade to each recommendation, an idea proposed by Mason and colleagues (5). In other words, each recommendation in a guideline could have two grades, one based on clinical outcomes and a second based on economic outcomes. Or ultimately, perhaps, a system could be devised to consider all evidence (clinical, economic, and humanistic) and provide one overall grade.

CHAPTER 2 LITERATURE REVIEW

Prostate Cancer

According to statistics provided by the American Cancer Society (3), the most common site of cancer among men in the United States is the prostate, with an estimated 230,110 men expected to have developed prostate cancer in 2004. Furthermore, prostate cancer is the second leading cause of cancer mortality, with an estimated 29,900 men expected to have died due to prostate cancer in 2004 (3).

Prostate cancer is often described in terms of prostate-specific antigen (PSA) level, clinical stage, and histologic grade, as all three characteristics have been found to be predictive of prostate cancer outcomes (6-9). Khan and Partin (10) report that the best understanding of a patient's extent of disease is arrived at by jointly considering the findings of the digital rectal examination (i.e., clinical stage), PSA, and Gleason score (i.e., histologic grade as determined by biopsy). In fact, studies conducted by Partin and others have led to the development, validation, and updating of nomograms, commonly referred to as Partin tables, which use the DRE findings, PSA level, and Gleason score to predict the true pathological stage of a patient's prostate cancer. The better understanding of the true severity of a patient's prostate cancer can then be used in making more educated decisions as to the appropriate treatment for the tumor.

Prostate-specific antigen (PSA) is used both as a screening tool and a tumor marker to identify the response of prostate cancer to treatment and the relapse of prostate cancer following treatment (11). In terms of screening, a PSA value equal to 4.0 ng/mL has

historically been viewed as the upper limit of normal. However, controversy surrounds this number as many patients with a PSA greater than 4.0 ng/mL do not have prostate cancer, and many patients with a PSA less than 4.0 ng/mL do have prostate cancer.

The clinical stage of a malignant tumor of the prostate is typically classified using the 2002 American Joint Committee on Cancer (AJCC) Tumor, Node, and Metastasis (TNM) Staging System for Prostate Cancer (4). The AJCC TNM Staging System for Prostate Cancer uses characteristics of the tumor itself, involvement of lymph nodes, and presence and extent of metastases to clinically stage prostate cancer (12). The Gleason score is a histological summary of the tumor pathology computed by summing the Gleason grade for the tumor's two most prevalent patterns of pathology. Each pathology pattern receives a grade ranging from one to five with one being well differentiated and 5 being undifferentiated. Thus the Gleason score ranges from two to ten (13).

Treatments for localized prostate cancer include radical prostatectomy, external beam radiotherapy, brachytherapy, and expectant management (watchful waiting) (14-20). For localized prostate cancer, available clinical evidence has not demonstrated a clear superiority of one treatment over all others and its management is described by many as controversial (8,14,18-23). A patient's treatment regimen could consist of any one or a combination of these treatment modalities depending on a variety of factors (16,24), including tumor stage (15,20,21,25,26), prostate-specific antigen level (15,16,20,25-27), histological grade of the tumor (15,16,20,21,25-28), patient age and life expectancy (15,21,26-28), comorbidities (15,21), cost(16), anticipated side effects, and patients' preferences regarding the various side effects (15,16,19).

Studies examining prostate cancer treatments have evaluated the various treatments using a number of endpoints. Endpoints evaluated include all-cause mortality, disease-specific mortality, and intermediate outcomes such as metastasis-free survival, clinical recurrence, and biochemical recurrence, among others. Our study focuses on prostate cancer-specific mortality.

Prostate Cancer-Specific Mortality

Four articles published since 1995 have compared the rate of prostate cancer-specific mortality of two or more of the three main treatment strategies for localized prostate cancer. Of the four studies comparing treatment strategies on the basis of prostate cancer-specific mortality data, one study compared expectant management and radical prostatectomy (18), one study compared radical prostatectomy and external beam radiotherapy (7), and two studies compared expectant management, radical prostatectomy, and radiotherapy (8,21).

Expectant management versus radical prostatectomy

Holmberg et al. report the results of a prospective trial in which patients with prostate cancer were randomized to either radical prostatectomy or watchful waiting (expectant management) (18). The study population consisted of 695 patients with prostate cancer classified as stage T0, T1 or T2 and Gleason score less than or equal to seven. Patients were on average approximately 65 years of age. The 5-year prostate cancer-specific mortality rate was 4.6% and 2.6% for patients randomized to watchful waiting and radical prostatectomy, respectively. The 8-year prostate cancer-specific mortality rate was 13.6% and 7.1% for patients randomized to watchful waiting and radical prostatectomy, respectively. The difference in 5-year prostate cancer-specific mortality rates between watchful waiting and radical prostatectomy was not statistically

significant. However, the difference in 8-year prostate cancer-specific mortality rates was statistically significant. Comparison of prostate cancer-specific survival using Cox proportional hazards regression models revealed an unadjusted hazard ratio of 0.5 (95% confidence interval: 0.27,0.91) comparing radical prostatectomy to watchful waiting and a hazard ratio 0.45 (95% confidence interval: 0.25, 0.84) when adjusted for tumor stage, Gleason score, and patient age.

Radical prostatectomy versus radiotherapy

Fowler et al. examined 5- and 10-year cause specific survival among 357 stage A2 or B prostate cancer patients treated with either radical prostatectomy or radiotherapy (7). The study was non-randomized and the choice of treatment typically followed an algorithm in which patients with a life expectancy greater than ten years, no pelvic lymph metastases, and no contraindication to surgery received radical prostatectomy and all others received radiotherapy. The treatment algorithm resulted in patients treated with radical prostatectomy and radiotherapy being similar in terms of tumor grade and prostate-specific antigen level but with radiotherapy patients being 4.5 years older on average than patients receiving radical prostatectomy. Five-year prostate cancer-specific mortality rates were 5% and 11% for patients treated with radical prostatectomy and radiotherapy, respectively. Ten-year prostate cancer-specific mortality rates were 14% and 33% for radical prostatectomy and radiotherapy, respectively. The difference in prostate cancer-specific mortality for patients treated with radical prostatectomy or radiotherapy was not significant at five or ten years.

Expectant management versus radical prostatectomy versus external beam radiotherapy

Barry et al. retrospectively assessed prostate cancer-specific survival among 2311 patients treated between 1971 and 1984 with expectant management, radical prostatectomy, or external beam radiotherapy (21). The 10-year prostate cancer-specific survival rates among patients with tumors graded as being Gleason scores of two to four were 94%, 83%, and 94% for patients treated with expectant management, external beam radiotherapy, and radical prostatectomy, respectively. The 10-year prostate cancer-specific survival rates for patients with tumors graded as being Gleason scores of five to seven were 75%, 72%, and 88% for expectant management, external beam radiotherapy, and radical prostatectomy, respectively. The 10-year prostate cancer-specific survival rates for patients with tumors graded as being Gleason score of eight to ten were 45%, 43%, and 64% for expectant management, external beam radiotherapy, and radical prostatectomy, respectively. Barry et al. did not perform analyses to determine if the survival rates of the treatments studied were statistically significantly different because of the incomparable nature of the cohorts in terms of age and comorbidities. Barry et al. also note the fact that the study population was diagnosed prior to the use of prostate-specific antigen testing and advancements in radiotherapy techniques, such as 3-dimensional conformal radiation.

Lu-Yao et al. used the Surveillance, Epidemiology, and End Results (SEER) database to estimate prostate cancer-specific mortality in patients treated with radical prostatectomy, radiotherapy, or watchful waiting (8). The study cohort included 59,876 men ranging from 50 to 70 years of age and diagnosed with prostate cancer between 1983 and 1992. For each treatment type, prostate cancer-specific mortality was estimated

within each of three grades of prostate cancer. The grades were defined on the basis of Gleason score with grade one including Gleason scores ranging from two to four, grade two including Gleason scores ranging from five to seven, and grade three including Gleason scores ranging from eight to ten.

As with any non-randomized study comparing radical prostatectomy to other treatment strategies, the study by Lu-Yao et al. was subject to selection bias and confounding (8). However, Lu-Yao and colleagues limit the impact of this bias by using a form of intent-to-treat analysis. More specifically, all patients treated with radical prostatectomy or undergoing a lymph node dissection were analyzed in the radical prostatectomy group regardless of whether the patient was found during prostatectomy or lymph node dissection to have disease that had spread beyond the prostate. Meanwhile, among patients undergoing radiation therapy, only those thought to have localized cancer were included. The reason for the difference is that among patients undergoing radiation therapy there is not the opportunity to detect the spread of disease as there is with patients undergoing radical prostatectomy and/or lymph node dissection. The decision as to whether the cancer was localized must be made at the same time for patients receiving the different treatments. Thus, the classification of the cancer as localized must be made at the time in which the treatment choice was made (i.e., before the information on whether the cancer has spread is obtained in the radical prostatectomy patients).

The 10-year prostate cancer-specific mortality rates determined using the intent-to-treat approach were 17% for radical prostatectomy, 24% for radiotherapy, and 18% for watchful waiting (8). In interpreting these results one must be reticent of the difference in mean age among the groups. Patients receiving radical prostatectomy, radiotherapy,

and watchful waiting were on average 65.8, 70.4, and 70.7 years of age. The impact of age on results is likely limited by using prostate cancer-specific mortality rather than overall mortality, however, there is still potential for difference in age to be partially responsible for the differential findings in prostate cancer-specific mortality. Lu-Yao et al. do not report whether the mortality differences were statistically different.

An additional important conclusion of Lu-Yao et al. (8) was the need for outcomes specific to each grade of prostate cancer. This conclusion was founded upon their finding that patients with grade one prostate cancer generally did well while patients with grade three prostate cancer generally did not do well. Lu-Yao et al. (8, p. 909) state “conclusions drawn from data pooled across cancer grades are therefore too optimistic for patients with grade three cancer and too pessimistic for patients with grade one disease.”

Summary of prostate cancer-specific mortality literature

Of the four studies described in which treatment strategies were compared in terms of prostate cancer-specific mortality, one was randomized and three were non-randomized. In assessing non-randomized studies, it is always necessary to consider the potential for a selection bias. Within the prostate cancer arena there is a particular concern that in non-randomized studies radical prostatectomy will errantly be found superior to other treatments as a result of a selection bias (i.e., patients with a better prognosis will receive prostatectomy and patients with a worse prognosis will receive radiotherapy, expectant management, or some other less physically demanding type of treatment because the individual with worse prognosis is perceived to not be able to withstand the physical stress of prostate surgery)(21). In addition to the need for awareness of a selection bias favoring radical prostatectomy, awareness must be

maintained for an information bias that could result in findings that errantly favor radical prostatectomy over other treatment strategies (8).

As for an information bias, there is often differential staging between patients undergoing radical prostatectomy and radiotherapy or watchful waiting (8). Typically only patients receiving radical prostatectomy receive pelvic lymph node dissection, which can identify involved nodes (indicating a more advanced stage of disease) and leading to a change in the course of treatment (i.e., the patient does not undergo prostatectomy and instead receives a different type of treatment). Patients treated with modalities other than radical prostatectomy do not typically undergo pelvic lymph node dissection and thus nodal involvement can be missed and result in a patient being classified with a less advanced disease than is actually the case. The resultant effect of this bias is that when comparing radical prostatectomy to other treatments among patients with disease that is *localized*, radical prostatectomy can appear more effective than other treatments because the other treatment groups are infiltrated with patients with non-localized disease.

As for a selection bias, patients receiving radical prostatectomy are typically healthier than patients undergoing radiotherapy or a watchful waiting strategy in terms of both general health (e.g., younger) and severity of prostate cancer (e.g., less advanced tumor stage) (29,30). Furthermore, as a result of the differential staging bias previously discussed, some patients scheduled to undergo radical prostatectomy will not undergo radical prostatectomy because of lymph node involvement, which is indicative of a more severe stage of disease and requires a different treatment strategy. Meanwhile, patients receiving other treatment options with more advanced disease will not be identified and

thus there will not be the opportunity to adjust their treatment strategies to strategies more appropriate for their more advanced disease state. The potential for such a bias was demonstrated by Lu-Yao and colleagues in which the treatment-received survival rate for patients treated with radical prostatectomy was significantly higher than that for the intent-to-treat survival rate for patients treated with radical prostatectomy (8).

Prostate Cancer Economics

Seven studies published since 1995 have examined treatment-specific prostate cancer cost. The majority of these studies have examined costs for either the initial treatment itself or first-year costs. One study modeled the impact of treatment failure over a 5-year period.

Penson et al. (31) used the CaPSURE database to assess the first-year treatment costs of treating prostate cancer with various treatment strategies. The CaPSURE database contains longitudinal data on the healthcare resources used by prostate cancer patients treated at 26 sites across the United States. In calculating the first-year treatment costs, Penson et al. (31) multiplied governmental unit reimbursement rates by the number of resource units consumed and summated across types of resources to arrive at the total first-year costs of each type of treatment.

According to Penson et al. (31), the cost of first-year treatment of prostate cancer using radical prostatectomy, radiotherapy, and watchful waiting in 1996 dollars was \$7,320, \$7,430, and \$484, respectively. Penson et al. (31) also examined the first-year costs of each treatment by stage of disease. The cost of radical prostatectomy was found to differ significantly across tumor stage, but the differences in cost of treatment across tumor stages for other treatment strategies failed to attain statistical significance. Penson et al. (31) note that the failure to attain statistically significant differences in costs

between differing severities of tumor stage could have been the result of small sample sizes as opposed to being truly equivalent. The cost of radical prostatectomy for patients with stage T1c, T2a/b, and T2c were \$6,881, \$7,216, and \$8,027, respectively.

Brandeis et al. (29) examined charges associated with prostate cancer by type of treatment among patients at least 65 years of age using Medicare charge data made available by the Health Care Financing Administration (HCFA). Medicare charges included in the analysis included those for work-up, treatment, and complications over a 1-year period. A total of 10,107 patients diagnosed with prostate cancer between 1993 and 1996 and included in the 5% random sample of Medicare beneficiaries made available by HCFA were included in the analysis.

Mean first-year charges for radical prostatectomy, external beam radiotherapy, brachytherapy, brachytherapy plus external beam radiotherapy, and radical prostatectomy plus external beam radiotherapy were \$19,019, \$15,937, \$15,301, \$24,407, and \$31,329, respectively (29). The only charges not statistically significantly different were brachytherapy versus external beam radiotherapy. Not surprisingly, patients treated with combination therapy (i.e., brachytherapy plus external beam radiotherapy or radical prostatectomy plus external radiotherapy), had the highest mean charges.

Burkhardt and colleagues (30) used the SEER-Medicare linked database to assess differences in costs associated with treatment of early-stage prostate cancer with either radical prostatectomy or external beam radiotherapy among Medicare beneficiaries enrolled in both Medicare Part A and Part B. Costs were assessed for a period of time beginning one month prior to diagnosis and ending nine months after diagnosis. The study included 4,956 radiotherapy patients in both the treatment-received and intent-to-

treat analyses, 4,847 radical prostatectomy patients in the treatment-received analysis, and 5,299 radical prostatectomy patients in the intent-to-treat analysis.

A variety of adjustments were used to ensure patients in the radiotherapy and radical prostatectomy cohorts were similar in terms of age and comorbidities (30). Regardless of comorbidity adjustment mechanism, patients treated with radical prostatectomy were found to have greater costs over the 10-month period beginning one month prior to diagnosis than patients treated with external beam radiotherapy. Using a comorbidity adjustment strategy in which a patient's average monthly Medicare expenditures were subtracted from each month in the 10-month cost assessment period, the cost of receiving either radical prostatectomy or external beam radiotherapy over a 10-month period were \$15,082 and \$11,377, respectively, using a treatment-received analysis. The intent-to-treat analysis resulted in the cost associated with receiving radical prostatectomy increasing to \$15,205. Regardless of type of analysis conducted – treatment-received or intent-to-treat – and whether an adjustment was made for comorbidities or not, Medicare expenditures over a 10-month period were significantly higher for prostate cancer patients treated with radical prostatectomy than those treated with external beam radiotherapy.

Perez et al. (32) examined reimbursement for treating patients with stage T1c or T2 prostate cancer using 3-dimensional conformal radiation therapy (3D-CRT), standard radiation therapy (SRT), and radical prostatectomy at a single institution. The average reimbursement for 3D-CRT, SRT, and radical prostatectomy during 1994 was \$13,823, \$10,864, and \$12,250, respectively.

Using a combination of institution-specific and literature-based efficacy data, Perez et al. (32) went a step further in assessing the cost of each treatment modality by incorporating the cost of five years of hormonal treatment consisting of a luteinizing hormone releasing hormone agonist and flutamide, a non-steroidal antiandrogen, for patients failing initial treatment. Assuming a 5% failure rate for patients treated 3D-CRT, and 20% for patients treated with SRT, and 10% for patients treated with radical prostatectomy, the cost of 3D-CRT, SRT, and radical prostatectomy increase to \$15,173, \$16,264, and \$16,405, respectively.

Wagner and colleagues (33) examined the hospital charges associated with treating patients with clinically localized prostate cancer with either radical prostatectomy or transperineal brachytherapy during 1996 and 1997. Among the 16 patients undergoing radical prostatectomy, the average total hospital charges were \$15,097, and among the 19 patients undergoing brachytherapy, the average total hospital charges were \$21,025. The resultant \$5,928 difference in the cost of hospital-related charges favoring radical prostatectomy was statistically significant.

In addition to comparing overall charges associated with radical prostatectomy and brachytherapy, Wagner et al. (33) compared the two treatments on a number of charge categories. The operative charges (i.e., anesthesia, operating room time, and operating room supplies) were found to be greater in patients undergoing radical prostatectomy than in those undergoing brachytherapy. Furthermore, the pharmacy and length of stay charges were significantly greater in radical prostatectomy patients. However, the charges for the radioactive seeds used in brachytherapy (\$7,033) overcame the savings associated with brachytherapy in operative, pharmacy, and length of stay charges.

Ciezki et al. (34) compared radical prostatectomy and brachytherapy in terms of perioperative costs. In assessing the perioperative costs among 404 patients treated with radical prostatectomy and 179 patients treated with brachytherapy between January 1, 1997 and October 30, 1998, Ciezki and colleagues (34) found brachytherapy to cost 85% to 105% more than radical prostatectomy.

Similar to Wagner et al. (33), Ciezki et al. (34) found the operative, pharmacy, and length of stay related charges to be significantly lower for brachytherapy than for radical prostatectomy. Yet, just as in the study by Wagner et al. (33), any savings in operative, pharmacy, and length of stay costs were overcome by the considerable costs of the radioactive seeds used in brachytherapy.

Kohan et al. (35) also compared the costs of radical prostatectomy and brachytherapy. Costs, including preoperative, operative, and postoperative costs, over a 1-year period were compared between 38 men with clinically localized prostate cancer undergoing radical prostatectomy and 22 men with clinically localized prostate cancer undergoing brachytherapy. All patients were treated at a single institution. Radical prostatectomy patients were younger (71.1 versus 61.2 years of age) and had less advanced tumors (52.6% stage T2 versus 68.1% stage T2). Furthermore, patients undergoing radical prostatectomy were more often treated with neoadjuvant hormonal therapy (45.5% versus 13.2%) than those undergoing radical prostatectomy.

Kohan and colleagues (35) found patients undergoing radical prostatectomy to have significantly greater operative charges (\$11,352.59 versus \$9,818.17) and significantly lower postoperative charges (\$1,007.20 versus \$2,285.20) than brachytherapy patients. However, preoperative and total charges were not found to be significantly different.

Total charges for radical prostatectomy and brachytherapy patients were \$13,904.60 and \$13,886.00, respectively.

The finding of no significant difference in overall charges between radical prostatectomy and brachytherapy by Kohan et al. (35) stands in contrast to the findings of Wagner et al. (33) and Czieki et al. (34) in which brachytherapy was found to be more expensive than radical prostatectomy. Kohan et al. (35) note that the discrepancy could be due to the fact that reimbursement in their institution was based on a flat rate specific to a procedure.

Grover and colleagues (36,37) developed a Markov model to forecast the clinical and economic burden of prostate cancer among Canadians. Data from the literature and population-based registries were used to estimate the efficacy and complications of prostate cancer for different tumor stages, histological grades, and treatment strategies (36). Canadian government fee schedules were used to apply costs to the resources used, and thus estimate the economic burden of prostate cancer among Canadian men (37). Unlike many of the other economic studies of prostate cancer, Grover et al. (37) estimated lifetime costs rather than costs for either just initial costs or just terminal costs. Unfortunately, Grover and colleagues (37) provide results only on an aggregate level; finding the total cost of prostate cancer among the population of Canadian men between ages 40 and 80 without prostate cancer in 1997 will cost \$9.76 billion (in 1996 Canadian dollars) over the lifetime of these men.

Burkhardt et al. (30, p. 2874) noted that their “study [did] not include costs beyond the initial treatment period, and these would be expected to differ if one treatment approach generates more long-term side effects than the other.” Given that the vast

majority of studies examining treatment-specific costs have been limited to the initial treatment period, there is a need for further study of treatment-specific costs over a longer period of follow-up. Beyond the impact of differing side-effect profiles on long-term costs, there is a need to consider the long-term costs of treatment failure. The consideration of long-term costs is also necessary in any comparison of treatment-specific costs in which watchful waiting is a potential treatment strategy. Our study will provide a substantial contribution to the existing literature by providing information on the long-term treatment-specific costs of prostate cancer.

Guidelines

Clinical practice guidelines are defined by the Institute of Medicine (38, p. 38) as “systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances.” Practice guidelines are developed with the intent of improving patients’ health outcomes (39-42), and have been shown repeatedly to improve health outcomes (42-44).

Based on the mass of new medical literature each week, it is impractical for any one clinician alone to assess all relevant literature for treating a condition. Thus, reviews summarizing evidence are necessary for a clinician to stay abreast of the relevant medical literature. Systematic reviews, such as Cochrane reviews, provide such summaries of the medical literature (45,46). Clinical guidelines go one step farther, providing recommendations for care based on the evidence summarized in systematic reviews (40,45,47,48). According to Cape and Barkham (41, p. 290), “guidelines set out the specific clinical *processes* that will lead to optimal *outcomes* for the specific circumstances.”

The production of practice guidelines surged throughout the decade of the 1990s, as evidenced by a PubMed search revealing more than 4,500 publications classified as practice guidelines indexed in the PubMed literature database by the end of 1999.

Guidelines are produced by a number of entities, including medical societies (general and specialty) and governments agencies (40,49,50). Guidelines are produced at local, regional, national, and international levels (49).

Development of Guidelines

The development of clinical practice guidelines is a significant undertaking in terms of both time and money (41,51-53); one report showed development costs of \$200,000 per guideline in the United States (54). Historically, guidelines were developed based on expert opinion (48,54); however guideline development has evolved into a process that is based on systematic reviews of evidence reported in the medical literature (41,48,54). Guidelines typically include practice recommendations based on both scientific evidence and expert opinion when there are not formal studies available (47,55).

Initially, a panel must be established to formulate the guidelines. The panel should be diverse in nature and representative of all parties the guidelines will impact, including users (e.g., physicians), patients, and experts in the clinical field (38,39,41,43,45,47,48,51,52,54). Additionally, guideline panels may include medical librarians, epidemiologists, statisticians, psychologists, communication specialists, health economists, and other experts in relevant methodologies (54).

Perhaps the most important step in developing guidelines is to assess the evidence on which practice recommendations will be made. Assessment of evidence is the base on which the guideline will be built (38). As such, the development of clinical practice

guidelines necessitates the performance of a systematic review of the evidence (43,51). Guidelines should include an overview of the evidence review, including how the evidence was located (e.g., PubMed search strategy) (38,39) and a description of inclusion criteria (i.e., study type) required for a study to be considered in the review of evidence (38,45,48).

An integral step in developing guidelines is formulating and reaching consensus on the practice recommendations to be included in the guideline (43,47,52,54). Efforts to reach consensus can be formal or informal (47,54), with informal consensus more likely to result in practice recommendations that are not based on scientific evidence (47). Formal consensus can be reached through a variety of techniques, such as a nominal group technique or a Delphi panel (40,47). According to the Appraisal of Guidelines, Research, and Evaluation in Europe (AGREE) Collaborative Group Practice (49, p. 1040), recommendations should be “explicitly linked” to the evidence on which they are based (38,47,54), and each recommendation should include a grade indicating the strength of the evidence (39,43,45,47,52,54). For example, a recommendation based on multiple randomized clinical trials would have a higher grade than a recommendation based purely on expert opinion.

Before disseminating guidelines, an external review process is undertaken (38,43,47,50,54). Shekelle et al. (52, p. 596) state that external review of guidelines is used to “ensure content validity, clarity, and applicability.” Ideally, the development of a guideline would also include a pre-testing phase (38). If a guideline is to remain valid over time, the guidelines must be updated as new evidence is discovered (51). Those in the guideline-development process should either determine when the guidelines will be

updated or determine conditions necessitating the update of the guidelines (e.g., a well-designed controlled trial reveals evidence contradictory to the guideline recommendations) (38,43,53).

Quality of Guidelines

As stated previously, the development of guidelines increased rapidly throughout the 1990s (42). So many guidelines were produced, that improving and assessing the quality of guidelines has become challenging (42). Agencies such as the Agency for Healthcare Quality and Research (AHRQ) in the United States and the National Health System in the United Kingdom are funding efforts to improve the quality of guideline development (56).

The Institute of Medicine (IOM) (38) developed a list of eight characteristics a clinical practice guideline would ideally meet: validity, reliability/reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, scheduled review, and documentation (38). These characteristics are self-explanatory with the possible exceptions of validity and reliability/reproducibility. The IOM (38, p. 58) states that valid clinical practice guidelines “lead to the health and cost outcomes projected for them.” Valid guidelines should include both statements on the strength of evidence used in the formulation of recommendations and an estimate of the impact of these recommendations on both health and cost outcomes (2). According to the IOM, reliable guidelines would result in the same care for a patient by two separate practitioners, and a separate guideline-development panel using the same development strategy and scientific evidence would replicate those guidelines (2).

Numerous studies have developed instruments to appraise the quality of a clinical practice guideline (2,39,40,42,57). The appraisal instruments range from a simple

checklist of three items (39) to a 46-item instrument developed by an Institute of Medicine committee (2). The Grilli 3-item checklist assesses whether a description was provided of the individuals developing the guideline, whether the search for evidence was described, and whether guideline recommendations were graded based on the level of supporting evidence (39). More comprehensive in nature, the IOM appraisal instrument has items explicitly assessing the degree to which seven of the IOM's eight desirable characteristics of a practice guideline are fulfilled (2). The eighth desirable characteristic, documentation, is implicitly assessed through many of the 46 questions.

National Comprehensive Cancer Network Prostate Cancer Guideline

The National Comprehensive Cancer Network (NCCN) is an alliance of 19 cancer centers, which constructs cancer treatment guidelines (58). The NCCN released its most recent version of treatment guidelines for prostate cancer in January 2004 (4). The goal of the guideline is to “extend life expectancy while minimizing treatment-related morbidity” (58, p. 15).

The NCCN prostate cancer clinical practice guideline appears to meet many of the characteristics desired in a guideline. The process used in the development of the guideline included clinical experts in the fields of medical and radiation oncology as well as urology; an extensive review and modification procedure was employed; recommendations were graded; evidence supporting the recommendation was cited; and an annual review process was planned and has been faithfully followed. One shortcoming of the guideline is its failure to outline the methods used to identify the literature that is used to support recommendations. The failure to outline the search process prevents the user from being able to judge whether the search for evidence was systematic and thorough.

The guideline makes recommendations for prostate cancer treatment on the basis of risk of recurrence and life expectancy (4). Risk of recurrence is classified as a function of the prostate specific antigen level, 2002 American Joint Committee on Cancer (AJCC) Tumor Node Metastasis (TNM) stage, and Gleason score (58).

Using the PSA value, clinical stage, and Gleason score, prostate cancer patients are classified as being at low, intermediate, high, or very high risk of recurrence (4). Patients with any positive nodes or any metastases are classified separately from patients without positive nodes or metastases and are not placed in a “risk of recurrence” group(4).

Patients at low risk are those with a PSA less than 10 nm/mL, a stage T1 to T2a tumor, or a Gleason score of 2 to 6. Those at intermediate risk are those with a PSA of 10 to 20 ng/mL, a stage T2b to T2c tumor, or a Gleason score of 7. Those at high risk are those with a PSA greater than 20 ng/mL, a stage T3a tumor, or a Gleason score of 8 to 10. Those at very high risk are those with a stage T3b to T4 tumor.

Treatment strategy recommendations for prostate cancer patients at low or intermediate risk of recurrence are further classified based on expected survival time (4). For patients at low risk of recurrence with a life expectancy less than ten years, the recommended treatment strategies are: expectant management; 3-dimensional conformal radiotherapy (3D-CRT); or brachytherapy. For patients at low risk of recurrence with a life expectancy greater than ten years, the recommended treatment strategies are: expectant management; 3D-CRT; brachytherapy; radical prostatectomy with pelvic lymph node dissection; or radical prostatectomy without pelvic lymph node dissection. For patients at intermediate risk of recurrence with a life expectancy less than ten years, the recommended treatment strategies are: expectant management; 3D-CRT; 3D-CRT

with brachytherapy; radical prostatectomy with pelvic lymph node dissection; or radical prostatectomy without pelvic lymph node dissection. For patients at intermediate risk of recurrence with a life expectancy greater than ten years, the recommended treatment strategies are: 3D-CRT; 3D-CRT with brachytherapy; radical prostatectomy with pelvic lymph node dissection; or radical prostatectomy without pelvic lymph node dissection.

The NCCN prostate cancer clinical practice guideline was used in our study to identify treatments recommended for patients with localized prostate cancer to be compared in terms of clinical effectiveness and cost.

Cost Estimation

One objective of our study was to estimate the difference in cost of treatment strategies for patients with localized prostate cancer (i.e. to compare treatment strategies recommended for patients at low or intermediate risk of prostate cancer recurrence according to the NCCN prostate cancer clinical practice guideline). In order for our findings regarding differences in cost to be valid, the methods used to estimate cost must be sound. Just as with effectiveness data, stochastic cost data collected as part of a randomized controlled trial or an observational study is often censored (59,60). As such, appropriate methods for estimating cost in the presence of censoring must be used.

Several methods have been suggested for the estimation of costs in the presence of censoring. Three methods previously used to estimate costs in the presence of censoring have now been determined to be invalid. The first of these methods was the simple mean of observed costs (60-62). The mean of observed costs does not incorporate costs occurring after censoring takes place and is thus biased in a downward manner. The second method used was the average costs among only patients who were not censored (60,61). This measure is also biased because it is representative of patients with shorter

survival times rather than the entire population of interest because patients with longer survival times are censored and not included in the estimate. The third method of estimating costs in the presence of censoring used standard survival analysis, replacing time to event with cost to event as the outcome being measured (60,61). The use of standard survival analysis methods to estimate costs in the presence of censoring was problematic because of a violation of the non-informative censoring assumption (59,60,63-65). The violation of the non-informative censoring assumption occurs because of a lack of independence between costs at the time of censoring and costs at the time of death (60,66). Lin (59, p. 36) notes the assumption is violated “even if the underlying censoring mechanism is purely random” because of “the inherent patient heterogeneity with respect to cost accumulation entails that the cumulative cost at the censoring time is positively correlated with the cumulative costs at the endpoint of interest.” In other words, there is a unique way in which each individual accumulates cost that results in costs at any time x being correlated with the costs at any time y for a given patient. And, as a result there is a correlation between a given individual’s costs at the time of censoring and at the time of death if the patient had not been censored. Thus, there is a violation of the assumption of non-informative censoring.

Fortunately, several methods have been developed to estimate costs in the presence of censoring that appear to work well. Two of the most commonly used methods are the Lin estimator and the Bang and Tsiatis estimator (62). The Lin estimator, also referred to as the direct method, divides the study period into k intervals, estimates the mean cost for patients alive at the start of the interval, and sums across the intervals the average cost of

each interval multiplied by the Kaplan-Meier estimator of surviving until the beginning of the interval (60).

The Bang and Tsiatis estimator is calculated using inverse weighting (65). The estimator is similar to the Lin estimator in that it divides the total time period into smaller intervals and estimates the cost within each interval. However, for patients dying within the interval, the cost is weighted by the inverse of the probability of not being censored at the time of death (64). Furthermore, if the patient survives until the end of the interval, the cost is weighted by the inverse of the probability of not being censored at the end of the interval.

The direct method (Lin's estimator) and the inverse-weighting method (Bang and Tsiatis's estimator) have been reported to be similar in terms of both variance and bias (64). Willan et al. (64) advocate use of the inverse-weighting method over the direct method because the direct method is more restrictive in terms of when censoring can take place. Similarly, provided that the intervals are relatively small, O'Hagan and Stevens (62) also recommend the use of the inverse-weighting method due to its consistency regardless of when censoring occurs. Equations 2-3 and 2-4, as reported by Willan et al. (64) estimate cost, v_j , in the presence of censoring using inverse-weighting and the variance, $V(v_j)$, of the cost estimate, respectively.

$$\hat{v}_j = \sum_{k=1}^K C_{jk} \quad (2-3)$$

$$\text{with, } C_{jk} = \left(\sum_{i=1}^{n_j} \frac{Y_{jki}}{\hat{G}_j(X_{jki}^*)} \right)^{-1} \sum_{i=1}^{n_j} \frac{Y_{jki} C_{jki}}{\hat{G}_j(X_{jki}^*)}$$

$$\text{and } Y_{jki} = \delta_{ji} + \bar{\delta}_{ji} I\{X_{ji} \geq a_{k+1}\}$$

$$\hat{V}(\hat{v}_j) = \sum_{i=1}^{n_j} \sum_{k=1}^K \sum_{l=1}^K Z_{jki}^{(c)} Z_{jli}^{(c)} \quad (2-4)$$

$$\text{with, } Z_{jki}^{(c)} = \frac{1}{n_j} \left(\frac{Y_{jki} (C_{jki} - C_{jk})}{G_j(X_{jki}^*)} + \bar{\delta}_{ji} B_{jki} - \sum_{l=1}^{n_j} \frac{\bar{\delta}_{jl} I\{X_{jl} \leq X_{ji}\} B_{jkl}}{R_{jl}} \right),$$

$$R_{ji} = \sum_{l=1}^{n_j} I\{X_{jl} \geq X_{ji}\}, \text{ and}$$

$$B_{jki} = \frac{1}{R_{ji}} \sum_{l=1}^{n_j} \frac{I\{X_{jkl}^* > X_{ji}\} Y_{jkl} (C_{jkl} - C_{jk})}{G_j(X_{jkl}^*)}$$

In cases where there is a need to adjust cost for one or more covariates, cost can be assessed using regression techniques that also incorporate inverse probability weighting to account for censoring. Cost is the dependent variable and independent variables include the treatment variable and any other covariates that might impact cost. Equations 2-5 and 2-6, as reported by Willan et al. (67), are used to estimate the coefficients and variance-covariance matrix for the independent variables. In Equations 2-5 and 2-6, Z_i is a p by 1 vector of individual i 's values for the p independent variables and $\hat{\beta}_k$ is a 1 by p vector of the coefficients for the p independent variables in the k^{th} time interval.

$$\hat{\beta}_k = \left(\sum_{i=1}^n \frac{\delta_{ki}^*}{\hat{G}(X_{ki}^*)} Z_i Z_i' \right)^{-1} \sum_{i=1}^n \frac{\delta_{ki}^* C_{ki}}{\hat{G}(X_{ki}^*)} Z_i \quad (2-5)$$

- n = number of individuals
- k = time-period (e.g., month or year)
- $\delta_{k,i}^* = 0$ if individual i was censored during year k , otherwise $\delta_{k,i}^* = 1$
- $X_i = \min(\text{time of event, censoring time})$
- $X_{k,i}^* = \min(X_i, k + 1)$
- $\hat{G}(X_{k,i}^*) = \text{Kaplan-Meier estimate of probability of not being censored at } X_{k,i}^*$
- $C_{k,i} = \text{observed cost for individual } i \text{ during time-period } k$

$$\hat{V}(\hat{\beta}) = n^{-1} \left(n^{-1} \sum_{i=1}^n Z_i Z_i' \right)^{-1} \left(n^{-1} \sum_{i=1}^n \sum_{k=1}^K \sum_{m=1}^K \zeta_{ki} \zeta_{mi}' \right) \left(n^{-1} \sum_{i=1}^n Z_i Z_i' \right)^{-1} \quad (2-6)$$

$$\zeta_{ki} = \left(\frac{\delta_{ki}^* (C_i - \hat{\beta}_k' Z_i)}{G(X_{ki}^*)} Z_i + \bar{\delta}_i F_{ki} - \sum_{j=1}^n \frac{\bar{\delta}_j I\{X_j \leq X_i\}}{R_j} F_{kj} \right)$$

- n = number of individuals
- k = time-period
- $\hat{\beta}_k$ is from Equation 2-5
- $\delta_{k,i}^* = 0$ if individual i was censored during time-period k , otherwise $\delta_{k,i}^* = 1$
- $X_i = \min(\text{time of event, censoring time})$ for individual i
- $X_j = \min(\text{time of event, censoring time})$ for individual j
- $X_{k,i}^* = \min(X_i, k + 1)$
- $\hat{G}(X_{k,i}^*) = \text{Kaplan-Meier estimate of probability of not being censored at } X_{k,i}^*$
- $C_i = \sum_{k=1}^K C_{k,i}$
- $\delta_i = 1$, if patient i experienced the event of interest, otherwise $\delta_i = 0$
- $\bar{\delta}_i = 1 - \delta_i$

$$F_{ki} = \frac{1}{R_i} \sum_{j=1}^n \frac{I\{X_{kj}^* > X_i\} \delta_{kj}^* (C_{kj} - \beta_k' Z_j)}{\hat{G}(X_{kj}^*)} Z_j$$

- n = number of individuals
- k = time period
- $\hat{\beta}_k$ is from Equation 2-6
- $\delta_{k,j}^* = 0$ if individual j was censored during time-period k , otherwise $\delta_{k,j}^* = 1$
- $X_i = \min(\text{time of event, censoring time})$ for individual i
- $X_j = \min(\text{time of event, censoring time})$ for individual j
- $X_{k,j}^* = \min(X_j, k + 1)$
- $\hat{G}(X_{k,j}^*) = \text{Kaplan-Meier estimate of probability of not being censored at } X_{k,j}^*$
- $C_{k,j} = \text{observed cost for individual } j \text{ during time-period } k$
- $\delta_j = 1$, if patient j experienced event of interest, otherwise $\delta_j = 0$
- $\bar{\delta}_j = 1 - \delta_j$

$$R_i = \sum_{j=1}^n I\{X_j \geq X_i\}$$

- n = number of individuals
- X_i = min(time of event, censoring time) for individual i
- X_j = min(time of event, censoring time) for individual j

Our study required the use of the regression techniques incorporating inverse weighting because it was not randomized (multiple confounding variables were identified) and the cost data was censored, and to the best of our knowledge is the first to estimate the cost of prostate cancer-specific healthcare using this technique.

Cost-effectiveness

Beyond summarizing differences between treatments in clinical effectiveness and cost, it can be useful to have a metric that jointly compares both differences in clinical effectiveness and cost. Cost-effectiveness is such a metric and is defined by Willan (68, p. 228) as “a quantitative method for comparing a new medical treatment to a relevant alternative (e.g., standard care) in terms of both costs and effectiveness.” Using the costs (in monetary units) and effects (in some clinical unit) of each treatment, comparisons are made to determine if one treatment dominates the other (69). Dominance occurs when one treatment is both more effective and less costly than the other (69,70). In cases where neither treatment dominates, an incremental cost-effectiveness ratio is calculated to compare the treatments in terms of cost-effectiveness (69). The incremental cost-effectiveness ratio is calculated as the ratio of the difference in the cost of the two interventions and the difference in the effectiveness of the two interventions (68,71). The calculated cost-effectiveness ratio is an estimate of the additional cost per unit of

effectiveness gained associated with using the more costly, more effective treatment rather than the less costly, less effective treatment (69).

Our study will not make any formal conclusions as to whether one treatment is cost-effective compared to another. Instead, for treatment comparisons identifying one treatment as both more effective and more costly, we will calculate and report the amount one must be willing to pay an additional unit of effectiveness for the more effective, more costly treatment to be cost-effective and will leave the decision as to whether the more effective, more costly treatment is cost-effective to the reader.

CHAPTER 3 METHODS

The methods of our study are presented in four parts. First, the methods used to establish cohorts for the comparison of treatment strategies recommended in the National Comprehensive Cancer Network (NCCN) prostate cancer clinical practice guideline for patients at low or intermediate risk of prostate cancer recurrence (i.e., patients with localized disease) are described. Second, the procedures used to assess and compare clinical effectiveness, in terms of prostate cancer-specific survival, of the strategies recommended for patients at low or intermediate risk of prostate cancer recurrence are presented. Third, the methods used to assess and compare the cost of prostate cancer-specific healthcare use the recommended treatment strategies are described. Finally, a description of the method used to assess the amount one must be willing to pay for a treatment that is both more effective and more costly to be cost-effective is presented.

Data Source

The source of data for our study was the linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database. The SEER portion of the SEER-Medicare linked database is a compilation of data collected by population-based cancer registries throughout the United States. The SEER registries collect demographic, clinical stage, histological grade, treatment, and outcomes data on all cancer diagnoses in a geographic region. The National Cancer Institute (NCI) administers the SEER program, and each registry is subjected to data audits to ensure the reliability and validity of the data (72). The NCI, in conjunction with the Centers for Medicare and Medicaid Services (CMS),

links the SEER cancer data with Medicare claims data for patients enrolled in Medicare. The linking of cancer registry data with Medicare claims data makes the SEER-Medicare database an ideal data source for studying the clinical and economic outcomes of cancer among an elderly population.

Establishment of Comparison Cohorts

Patients included in the study were: at low or intermediate risk of prostate cancer recurrence (defined below); managed with an initial treatment strategy recommended in the NCCN prostate cancer clinical practice guideline; diagnosed between 1992 and 1999; continuously eligible for Medicare (Parts A and B) from the time of diagnosis until either death or the end of the study period (i.e., December 31, 2002); and not enrolled in a Medicare health maintenance organization. After identifying patients meeting the inclusion criteria, the patients were divided into cohorts defined on the basis of the initial treatment strategy received. The initial treatment strategies compared were expectant management, external beam radiotherapy, brachytherapy, prostatectomy, and external beam radiotherapy with brachytherapy.

Risk of Recurrence

The National Comprehensive Cancer Network categorization of prostate cancer patients into risk of prostate cancer recurrence groups is based upon biochemical, clinical, and histological criteria (4). The biochemical, clinical, and histological criteria used are the prostate specific antigen (PSA) level, the 2002 American Joint Committee on Cancer (AJCC) Tumor, Node, and Metastasis (TNM) Staging System for Prostate Cancer classification, and the Gleason score. Patients at low risk are those with a PSA less than 10 ng/mL, a stage T1 to T2a tumor, or a Gleason score of 2 to 6. Those at intermediate

risk are those with a PSA of 10 to 20 ng/mL, a stage T2b to T2c tumor, or a Gleason score of 7.

The SEER database was used to classify patients' risk of recurrence. The SEER database does not contain data on PSA values for patients diagnosed with prostate cancer prior to 1998. Thus, our study only used tumor stage and grade in classifying a patient's risk of recurrence due to constraints imposed by the available data. The clinical extension component of the extent of disease variable in the SEER database provided the patient's TNM stage. The grade component of the morphology variable in the SEER database provided a proxy for the patient's Gleason score. Within the SEER database, the grade component of the morphology variable is classified as one for patients with a Gleason score of two, three, or four. If the Gleason score is five, six, or seven, the grade component of the morphology variable is classified as two. If the Gleason score is eight, nine, or ten, the grade component of the morphology variable is classified as three.

As noted above, patients at low or intermediate risk of recurrence were combined for the comparison of treatments rather than comparing treatments separately for those at low risk of recurrence and those at intermediate risk of recurrence. The decision to group those at low and intermediate recurrence risk together before making treatment comparisons was made because the SEER database does not provide the actual Gleason score and the grade component variable used in our study does not allow for discrimination between the Gleason scores that would place an individual at low recurrence risk (i.e., 2 to 6) or intermediate recurrence risk (i.e., 7). An additional advantage of combining the low and intermediate recurrence risk patients was the

increase in the power of the comparisons to find a difference between compared treatments because of the increased sample size.

Initial Treatment

The initial treatment strategy received by each prostate cancer (ICD-9-CM code 185.xx) patient was determined using both the treatment information provided in the SEER and Medicare claims databases. The treatment information provided in the SEER database is any treatment received within four months of diagnosis. Physician's Current Procedural Terminology (CPT), Health Care Financing Administration Common Procedure Coding System (HCPCS), and ICD9-CM procedure codes (Tables 3-1 to 3-6) on claims submitted to Medicare for services provided during the period beginning one month prior to and ending four months after prostate cancer diagnosis were also used in determining the initial treatment. The decision rules for determining the initial treatment strategy received were as follows:

- a patient was deemed to have received prostatectomy if the SEER data indicated the patient had a prostatectomy AND the patient did not have a claim during the period beginning one month prior to and ending four months after prostate cancer diagnosis with: A) a CPT/HCPCS code (Table 3-1) or ICD9-CM procedure code (92.2x: Therapeutic radiology and nuclear medicine) for radiotherapy (external beam or brachytherapy); B) a CPT/HCPCS code (Table 3-2) or ICD9-CM procedure code (Table 3-3) for androgen deprivation (surgical or chemical); or, C) a CPT/HCPCS code (Table 3-4) for any other type of prostate cancer treatment
- a patient was deemed to have received external beam radiation if the SEER data indicated the patient received external beam radiotherapy AND the patient did not have a claim during the period beginning one month prior to and ending four months after prostate cancer diagnosis with: A) a CPT/HCPCS code (Table 3-5) or ICD9-CM procedure code (Table 3-6) for prostatectomy; B) a CPT/HCPCS code (Table 3-2) or ICD9-CM procedure code (Table 3-3) for androgen deprivation (surgical or chemical); or, C) a CPT/HCPCS code (Table 3-4) for any other type of prostate cancer treatment
- a patient was deemed to have received brachytherapy if the SEER data indicated the patient received brachytherapy AND the patient did not have a claim during the period beginning one month prior to and ending four months after prostate cancer

diagnosis with: A) a CPT/HCPCS code (Table 3-5) or ICD9-CM procedure code (Table 3-6) for prostatectomy; B) a CPT/HCPCS code (Table 3-2) or ICD9-CM procedure code (Table 3-3) for androgen deprivation (surgical or chemical); or, C) a CPT/HCPCS code (Table 3-4) for any other type of prostate cancer treatment

- a patient was deemed to have received external beam radiation with brachytherapy if the SEER data indicated the patient received external beam radiotherapy with brachytherapy AND the patient did not have a claim during the period beginning one month prior to and ending four months after prostate cancer diagnosis with: A) a CPT/HCPCS code (Table 3-5) or ICD9-CM procedure code (Table 3-6) for prostatectomy; B) a CPT/HCPCS code (Table 3-2) or ICD9-CM procedure code (Table 3-3) for androgen deprivation (surgical or chemical); or, C) a CPT/HCPCS code (Table 3-4) for any other type of prostate cancer treatment
- a patient was deemed to have received expectant management if the SEER data indicated the patient did not receive prostatectomy, external beam radiation, or brachytherapy AND the patient did not have a claim during the period beginning one month prior to and ending four months after prostate cancer diagnosis with: A) a CPT/HCPCS code (Table 3-1) or ICD9-CM procedure code (92.2x: Therapeutic radiology and nuclear medicine) for radiotherapy (external beam or brachytherapy); B) a CPT/HCPCS code (Table 3-5) or ICD9-CM procedure code (Table 3-6) for prostatectomy; C) a CPT/HCPCS code (Table 3-2) or ICD9-CM procedure code (Table 3-3) for androgen deprivation (surgical or chemical); or, D) a CPT/HCPCS code (Table 3-4) for any other type of prostate cancer treatment

While the NCCN prostate cancer clinical practice guideline calls for the use of 3-dimensional conformal radiotherapy rather than 2-dimensional radiotherapy, it was not possible based on the information included in the SEER database to distinguish between the two variations of external beam radiotherapy. Furthermore, while procedure codes used to bill Medicare distinguish between 2- and 3-dimensional radiotherapy, examination of the data led to a lack of confidence in the reliability of the coding to distinguish between 2- and 3-dimensional radiotherapy. Thus, 2- and 3-dimensional beam radiotherapy were grouped together as external beam radiotherapy in all analyses.

Comparisons of prostate cancer-specific survival and cost of prostate cancer-specific healthcare use were based only on the initial treatment strategy (i.e., treatment received in the first four months following diagnosis). Treatment received after the first

four months did not impact the initial treatment strategy groupings used for comparing prostate cancer-specific survival and cost of prostate cancer-specific healthcare use.

Propensity Scores

As with any study without randomization, our study was subject to selection bias and could have been influenced by multiple observed and non-observed confounders. Our study used a multivariate analysis with an individual's propensity score (explained below) included as a covariate to control for the effect of variables believed to be confounders. The propensity score is the probability of a patient receiving treatment x rather than treatment y given the patient's observed values on the characteristics thought to be potential confounders (73).

The propensity score was estimated using multiple logistic regression with the dependent variable being treatment received and the independent variables being hypothesized confounding variables. The hypothesized confounders used in the logistic regression as independent variables were: SEER registry (an indicator of geographic area), age at diagnosis, race, year of prostate cancer diagnosis, tumor stage, tumor grade, urban/rural classification, and Charlson comorbidity score. A confounding variable is a variable related to both the treatment received and the outcome of interest. Each of the variables believed to be confounders included in the logistic regression estimating the propensity score were related to both the treatment received and prostate cancer-specific survival, except for the Charlson comorbidity score (see Chapter 4). Following estimation of the model, each individual patient's propensity score was calculated. A separate propensity score model was developed for each pair of treatments compared:

- expectant management vs. external beam radiotherapy
- expectant management vs. brachytherapy

- expectant management vs. prostatectomy
- expectant management vs. external beam radiotherapy with brachytherapy
- external beam radiotherapy vs. brachytherapy
- external beam radiotherapy vs. prostatectomy
- external beam radiotherapy vs. external beam radiotherapy with brachytherapy
- brachytherapy vs. prostatectomy
- brachytherapy vs. external beam radiotherapy with brachytherapy
- prostatectomy vs. external beam radiotherapy with brachytherapy

The propensity score calculated for a comparison of two treatments can be used to control for differences between groups in three ways: matching; stratification; and inclusion as a covariate in a regression model. In order to retain maximum power to detect a difference in prostate cancer-specific survival and cost of prostate cancer-specific healthcare use between treatment strategies, the propensity score was used as a covariate in the regression models assessing the relation between treatment and outcome because inclusion of the propensity score in a multivariate model does not decrease sample size, which occurs with both matching and stratification.

Clinical Effectiveness

The clinical effectiveness of each treatment strategy was defined by the estimated survival function of the treatment strategy at 5-years (a standard time frame for examining cancer survival). The methods of Kaplan and Meier (74) were used to estimate each treatment-specific survival function. Equation 3-1 is the Kaplan-Meier estimate of the survival curve with d_j being the number of deaths due to prostate cancer at time j and n_j being the number of individuals at risk of death at time j .

$$\hat{S}(t) = \prod_{j=1}^k \exp(d_j / n_j) \quad (3-1)$$

In estimating the survival function, patients with prostate cancer listed as the cause of death in the SEER database were treated as events, and patients dying due to

causes other than prostate cancer or alive at the end of 5-year follow-up period were treated as censored observations. Patients dying due to prostate cancer were identified by the cause of death listed in the SEER database, which uses state death certificates to classify a patient's cause of death. (75). The SEER database classifies patients with ICD-9 code 185 or ICD-O-2 code C619 on the death certificate as dying due to prostate cancer.

The effect of the initial treatment strategy received on prostate cancer-specific survival was determined using the Cox proportional hazards model. Equation 3-2 presents the Cox proportional hazards model used in comparing each pair of treatments. In Equation 3-2, trt_i is a dummy variable indicating individual i 's initial treatment strategy and ps_i is individual i 's calculated propensity score.

$$h_i(t) = \exp(\beta_{trt} * trt_i + \beta_{ps} * ps_i)h_0(t) \quad (3-2)$$

The Wald statistic was used to test whether a statistically significant difference in the hazard of death due to prostate cancer existed between the treatments being compared controlling for the variables included in the propensity score (i.e., SEER registry, urban/rural classification, race, tumor stage, tumor grade, year of diagnosis, age at diagnosis, and Charlson comorbidity score). The *a priori* significance level was set at 0.05.

Cost of Treatment

The cost of interest was that of prostate cancer-specific healthcare use over the 5-year period beginning with prostate cancer diagnosis. Several key tasks had to be accomplished in estimating this cost. First, the amount of all healthcare costs incurred by prostate cancer patients that are attributable to prostate cancer was determined. In other

words, prostate cancer-related and non-prostate cancer-related costs were separated. Second, in order for the testing of differences in costs between two treatment strategies to be fair, the groups had to be similar in terms of factors that might influence the accrual of costs. Third, the estimation of costs had to take into account the presence of censoring in the cohort of prostate cancer patients being used to estimate the cost of prostate cancer-specific healthcare use.

Initially, the methods proposed by Brown and colleagues (76), in which total healthcare costs are determined for both cancer patients and matched controls were used to estimate prostate cancer attributable costs. However, the estimates did not appear stable, and an alternate approach (described below) was instead used to estimate the cost of prostate cancer-specific healthcare use.

Rather than using prostate cancer and matched non-cancer patients to estimate the cost of prostate cancer-specific healthcare use, the alternate approach used only prostate cancer patients in the estimation of costs. The alternate approach used the ICD-9-CM diagnosis codes included as support for a claim when submitted to Medicare to determine if the cost associated with the claim was related to prostate cancer. If a claim included ICD-9-CM code 185.xx (the diagnosis code for prostate cancer), the cost associated with the claim was deemed to be related to prostate cancer. The cost of each claim was adjusted to year 2004 US dollars using the medical component of the Consumer Price Index.

In order to balance the groups on important covariates and account for the presence of censoring, the regression techniques proposed by Lin (59) and Willan et al. (67) were used. The regression method described by Lin (59) and Willan et al. (67) divides the

time period of interest into smaller time intervals for which cost data is available and estimates a separate regression for each of the time intervals. The method allows an individual's error terms to be correlated across each of the separate regressions for different time intervals(59). Our study estimated five regressions equations (i.e., one regression for each of five 1-year time intervals). Each equation regressed an individual's observed cost for prostate cancer-specific healthcare use on the treatment received and the individual's calculated propensity score. Equation 3-3 is an example of one of the regression equations.

$$C_{k,i} = \beta_{icpt,k} * 1 + \beta_{trt,k} * trt_i + \beta_{ps,k} * ps_i + \epsilon_{k,i} \quad (3-3)$$

In Equation 3-3, $C_{k,i}$ is individual i 's observed cost of prostate cancer-specific healthcare use in year k , trt_i is a dummy variable indicating individual i 's initial treatment strategy, and ps_i is individual i 's calculated propensity score. Prior to carrying out the regression, a variable was created and set to equal "1" for each individual. The creation of the variable set to equal "1" for all individuals is used to obtain an intercept value ($\beta_{icpt,k}$) which provides an estimate of the k^{th} year cost of prostate cancer-specific healthcare use associated with being initially treated with the treatment coded as zero on the trt dummy variable and having a propensity score of zero. The k^{th} year cost for prostate cancer-specific healthcare use for an individual receiving the treatment coded one and having a propensity score of zero is the sum of $\beta_{icpt,k}$ and $\beta_{trt,k}$. The k^{th} year cost of prostate cancer-specific healthcare use for any given propensity score can be calculated by adding the product of the individuals propensity score and $\beta_{ps,k}$ to $\beta_{icpt,k}$ if the patient received the treatment coded zero or to the sum of $\beta_{icpt,k}$ and $\beta_{trt,k}$ if the patient received the treatment coded one. Equation 3-4 is used to calculate the k^{th} year cost ($C_{0,k}$)

for an individual receiving the treatment coded as zero but having a propensity score indicating the individual was equally likely to have received the treatment coded as one. Equation 3-5 is used to calculate the k^{th} year cost ($C_{1,k}$) for an individual receiving the treatment coded as one but having a propensity score indicating the individual was equally likely to have received the treatment coded as zero.

$$C_{0,k} = \beta_{\text{icpt},k} + (0.5 * \beta_{\text{ps},k}) \quad (3-4)$$

$$C_{1,k} = \beta_{\text{icpt},k} + \beta_{\text{trt},k} + (0.5 * \beta_{\text{ps},k}) \quad (3-5)$$

As noted above, the same regression was also performed for years two, three, four, and five. The 5-year cost (C_0) for an individual receiving the treatment coded zero but having a propensity score indicating the individual was equally likely to have received the treatment coded as one is calculated using Equation 3-6. The 5-year cost (C_1) for an individual receiving the treatment coded one but having a propensity score indicating the individual was equally likely to have received the treatment coded as zero is calculated using Equation 3-7.

$$C_0 = \beta_{\text{icpt},1} + (0.5 * \beta_{\text{ps},1}) + \beta_{\text{icpt},2} + (0.5 * \beta_{\text{ps},2}) + \beta_{\text{icpt},3} + (0.5 * \beta_{\text{ps},3}) + \beta_{\text{icpt},4} + (0.5 * \beta_{\text{ps},4}) + \beta_{\text{icpt},5} + (0.5 * \beta_{\text{ps},5}) \quad (3-6)$$

$$C_1 = \beta_{\text{icpt},1} + \beta_{\text{trt},1} + (0.5 * \beta_{\text{ps},1}) + \beta_{\text{icpt},2} + \beta_{\text{trt},2} + (0.5 * \beta_{\text{ps},2}) + \beta_{\text{icpt},3} + \beta_{\text{trt},3} + (0.5 * \beta_{\text{ps},3}) + \beta_{\text{icpt},4} + \beta_{\text{trt},4} + (0.5 * \beta_{\text{ps},4}) + \beta_{\text{icpt},5} + \beta_{\text{trt},5} + (0.5 * \beta_{\text{ps},5}) \quad (3-7)$$

If β is defined as the $\{\beta_{\text{icpt},k} \beta_{\text{trt},k} \beta_{\text{ps},k}\}$ vector and Z is defined as the $\{1, \text{trt}_i, \text{ps}_i\}$ vector, the coefficients in Equation 3-3 can be estimated using Equation 3-8 from Willan et al. (67), and the variance-covariance matrix for β can be estimated using Equation 3-9 from Willan and colleagues (67). The value of $\delta_{k,i}^* / \hat{G}(X_{k,i}^*)$ in Equation 3-8 is the inverse probability of censoring weight described in Chapter 2 that has been shown to result in a consistent and non-biased estimate of cost in the presence of censoring.

$$\hat{\beta}_k = \left(\sum_{i=1}^n \frac{\delta_{k,i}^*}{\hat{G}(X_{k,i}^*)} \{1, trt_i, ps_i\} \{1, trt_i, ps_i\}' \right)^{-1} \sum_{i=1}^n \frac{\delta_{k,i}^* C_{k,i}}{\hat{G}(X_{k,i}^*)} \{1, trt_i, ps_i\} \quad (3-8)$$

- n = number of individuals
- k = year
- $\delta_{k,i}^* = 0$ if individual i was censored during year k , otherwise $\delta_{k,i}^* = 1$
- $X_i = \min(\text{year of prostate cancer-specific death, censoring year})$
- $X_{k,i}^* = \min(X_i, k + 1)$
- $\hat{G}(X_{k,i}^*) = \text{Kaplan-Meier estimate of probability of not being censored at } X_{k,i}^*$
- $C_{k,i} = \text{observed cost for individual } i \text{ during year } k$
- $trt_i = \text{individual } i\text{'s value for the trt dummy variable}$
- $ps_i = \text{individual } i\text{'s propensity score}$

$$\hat{V}(\hat{\beta}) = n^{-1} \hat{A}^{-1} \hat{B} \hat{A}^{-1} \quad (3-9)$$

- n = number of individuals
- \hat{A} is defined below
- \hat{B} is defined below

$$\hat{A} = n^{-1} \sum_{i=1}^n \{1, trt_i, ps_i\} \{1, trt_i, ps_i\}'$$

- n = number of individuals
- $trt_i = \text{individual } i\text{'s value for the trt dummy variable}$
- $ps_i = \text{individual } i\text{'s propensity score}$

$$\hat{B} = n^{-1} \sum_{i=1}^n \sum_{k=1}^K \sum_{m=1}^K \hat{\xi}_{ki} \hat{\xi}_{mi}'$$

- n = number of individuals
- K = number of time periods (5 in our study)
- $\hat{\xi}_{ki}$ is defined below

$$\hat{\xi}_{ki} = \frac{\delta_{k,i}^* \left(C_i - \hat{\beta}_k' \{1, trt_i, ps_i\} \right)}{G(X_{k,i}^*)} \{1, trt_i, ps_i\}_i + \bar{\delta}_i F_{k,i} - \sum_{j=1}^n \frac{\bar{\delta}_j I\{X_j \leq X_i\}}{R_j} F_{k,j}$$

- n = number of individuals

- $k = \text{year}$
- $\hat{\beta}_k$ is from Equation 3-6
- $\delta_{k,i}^* = 0$ if individual i was censored during year k , otherwise $\delta_{k,i}^* = 1$
- $X_i = \min(\text{year of prostate cancer-specific death, censoring year})$ for individual i
- $X_j = \min(\text{year of prostate cancer-specific death, censoring year})$ for individual j
- $X_{k,i}^* = \min(X_i, k + 1)$
- $\hat{G}(X_{k,i}^*) = \text{Kaplan-Meier estimate of probability of not being censored at } X_{k,i}^*$
- $C_i = \sum_{k=1}^K C_{k,i}$
- $\delta_i = 1$, if patient i died due to prostate cancer, otherwise $\delta_i = 0$
- $\bar{\delta}_i = 1 - \delta_i$
- $\text{trt}_i = \text{individual } i\text{'s value for the trt dummy variable}$
- $\text{ps}_i = \text{individual } i\text{'s propensity score}$
- R_j is defined below
- $F_{k,i}$ is defined below

$$F_{k,i} = \frac{1}{R_i} \sum_{j=1}^n \frac{I\{X_{k,j}^* > X_i\} \delta_{k,j}^* \left(C_{k,j} - \beta_k' \{1, \text{trt}_j, \text{ps}_j\} \right)}{\hat{G}(X_{k,i}^*)} \{1, \text{trt}_j, \text{ps}_j\}$$

- $n = \text{number of individuals}$
- $k = \text{year}$
- $\hat{\beta}_k$ is from Equation 3-6
- $\delta_{k,j}^* = 0$ if individual j was censored during year k , otherwise $\delta_{k,j}^* = 1$
- $X_i = \min(\text{year of prostate cancer-specific death, censoring year})$ for individual i
- $X_j = \min(\text{year of prostate cancer-specific death, censoring year})$ for individual j
- $X_{k,j}^* = \min(X_j, k + 1)$
- $\hat{G}(X_{k,j}^*) = \text{Kaplan-Meier estimate of probability of not being censored at } X_{k,j}^*$
- $C_{k,j} = \text{observed cost for individual } j \text{ during year } k$
- $\delta_j = 1$, if patient j died due to prostate cancer, otherwise $\delta_j = 0$
- $\bar{\delta}_j = 1 - \delta_j$
- $\text{trt}_j = \text{individual } j\text{'s value for the trt dummy variable}$
- $\text{ps}_j = \text{individual } j\text{'s propensity score}$
- R_i is defined below

$$R_i = \sum_{j=1}^n I\{X_j \geq X_i\}$$

- n = number of individuals
- X_i = min(year of prostate cancer-specific death, censoring year) for individual i
- X_j = min(year of prostate cancer-specific death, censoring year) for individual j

The treatment-specific 5-year cost of prostate cancer-specific healthcare use reported in Chapter 4 for each treatment was calculated to be representative of that for an individual equally likely to receive either of the two treatments in the comparison (i.e., the propensity score was set to equal 0.5). The Wald statistic was used to test whether a statistically significant difference in the cost of prostate cancer-specific healthcare use existed between the treatments being compared controlling for the variables included in the propensity score. The *a priori* significance level was set at 0.05.

Cost-effectiveness

For any treatment comparison in which one treatment was both more effective and more costly, we calculated the incremental cost-effectiveness ratio (ICER) using Equation 3-8. As noted in Chapter 2, the incremental cost-effectiveness ratio provides an understanding of how much one must be willing to pay for an additional unit of effectiveness for the more effective, more costly treatment to be cost effective compared to the less effective, less costly treatment. We chose not to make a conclusion as to whether a more effective, more costly treatment is cost effective. Instead, we have reported the incremental cost effectiveness ratio in terms of the cost one must be willing to pay to prevent one death due to prostate cancer over a 5-year period in order to make the more effective, more costly treatment cost effective. It is up to the reader to determine whether the cost to prevent one death due to prostate cancer over a 5-year period makes the more effective, more costly treatment cost effective or not. In Equation 3-8, $\hat{\Delta}_c$ was the difference in the 5-year cost of prostate cancer-specific healthcare use

between the treatments being compared. The difference in effectiveness, $\hat{\Delta}_e$, was determined using the estimate of the 5-year survival function for the less effective treatment and the hazard ratio that adjusts for differences in the characteristics included in the propensity score (SEER registry, urban/rural classification, race, tumor stage, etc.).

$$ICER = \frac{\hat{\Delta}_c}{\hat{\Delta}_e} \quad (3-8)$$

Table 3-1. Radiotherapy (external beam or brachytherapy) CPT/HCPCS codes

CPT/HCPCS	Description
76078	radiographic absorptiometry
76950	ultrasonic guidance for placement of radiation therapy fields
76965	ultrasonic guidance for interstitial radioelement application
77261-77264	therapeutic radiology treatment planning
77280, 77285, 77290, 77295	therapeutic radiology simulation-aided field setting
77299	unlisted procedure, therapeutic radiology clinical treatment planning
77300	basic radiation dosimetry calculation
77305, 77310, 77315	teletherapy, isodose plan
77321	special teletherapy port plan
77326-77328	brachytherapy isodose plan
77331	special dosimetry
77332-77334	treatment devices, design and construction
77336	continuing medical physics consultation
77370	special medical radiation physics consultation
77380, 77520	proton treatment delivery
77399	unlisted procedure, medical radiation physics consultation
77400-77416	radiation treatment delivery
77417	therapeutic radiology port films
77419, 77420, 77424, 77425	weekly radiation therapy management
77427, 77430-77435	radiation treatment management
77470	special radiation treatment procedure
77499	unlisted procedure, therapeutic radiology treatment management
77750	intracavitary radiation source application
77761-77263	intracavitary radiation source application
77776-77778	interstitial radiation source application
77781-77784	remote afterloading high intensity brachytherapy
77789	surface application of radiation source
77790	supervision, handling, loading of radiation source
77799	unlisted procedure, clinical brachytherapy
79900	provide therapeutic radiopharmaceuticals

Table 3-2. Androgen deprivation CPT/HCPCS codes

HCPCS/CPT	Description
54520, 54521, 54529, 54530	remove testis
J9202	goserelin
J1950, J9217, J9218	leuprolide

Table 3-3. Androgen deprivation ICD9-CM procedure codes

ICD9-CM Procedure Code	Description
62	Operations on testes
62.0	Incision of testis
62.2	Excision or destruction of testicular lesion
62.3	Unilateral orchiectomy
62.4x	Bilateral orchiectomy

Table 3-4. Other prostate cancer treatment CPT/HCPCS codes

CPT Code	Description
53850	transurethral destruction of prostate tissue, by microwave thermotherapy
53852	transurethral destruction of prostate tissue, by radiofrequency thermotherapy
55860	exposure of prostate, any approach, for insertion of radioactive substance
77600	hyperthermia, externally generated; superficial
77605	hyperthermia, externally generated; deep
77610	hyperthermia generated by interstitial probes (5 or fewer applicators)
77615	hyperthermia generated by interstitial probes (more than 5 applicators)

Table 3-5. Prostatectomy CPT/HCPCS codes

CPT/HCPCS	Description
52601	transurethral electro-surgical resection of prostate
52612, 52614, 52620, 52630	transurethral resection of prostate
52647	non-contact laser coagulation of prostate
52648	contact laser vaporization with or without transurethral resection of prostate
52650	transurethral prostate surgery
55810, 55812, 55815, 55840, 55842, 55845	extensive prostate surgery
55801, 55821, 55831	removal of prostate
G0160	cryosurgical ablation of localized prostate cancer

Table 3-6. Prostatectomy ICD9-CM procedure codes

ICD9-CM Procedure Code	Description
60	Operations on prostate and seminal vesicles
60.0	Incision of prostate
60.2x	Transurethral prostatectomy
60.3	Suprapubic prostatectomy
60.4	Retropubic prostatectomy
60.5	Radical prostatectomy
60.6x	Other prostatectomy
60.8x	Incision or excision of periprostatic tissue
60.9x	Other operations on prostate

CHAPTER 4 RESULTS

A total of 161,557 men residing in Surveillance, Epidemiology, and End Results (SEER) geographic areas were diagnosed with prostate cancer between 1992 and 1999. The elimination of individuals without continuous eligibility, individuals participating in a Medicare health maintenance organization, individuals with periods of time in which the individual was not enrolled in Medicare between the time of diagnosis and death, and those not at either low or intermediate risk of recurrence reduced our study sample to 38,334 individuals.

The average age among those patients at either low or intermediate risk of prostate cancer recurrence was 74.0 (SD = 5.6). Of the 38,334 prostate cancer cases, 85.7% of the individuals were Caucasian, 8.5% were African-American, 1.5% were Hispanic, 2.5% were Asian, 0.2% were Native American, and 1.6% were classified as other or unknown. Seven hundred sixteen individuals died due to prostate cancer within five years of diagnosis. SEER registry (an indication of the individual's geographic location), race (Table 4-1), urban/rural classification (Table 4-2), tumor grade (Table 4-3), tumor stage (Table 4-4), diagnosis year (Table 4-5), and age at diagnosis (77.3 for patients dying due to prostate cancer within five years of diagnosis and 73.9 for patients not dying due to prostate cancer within five years of diagnosis) were found to be related to prostate cancer-specific death ($p < 0.05$ for each). The difference in Charlson comorbidity score, which increases with the number illnesses a patient has, for those dying due to prostate

cancer (0.333) and those not dying due to prostate cancer (0.329) within five years of diagnosis was not significantly different ($p = 0.07$).

Only 12,292 of the 38,334 prostate cancer patients at low or intermediate risk of recurrence were initially treated with one of the treatment strategies recommended in the National Comprehensive Cancer Network (NCCN) prostate cancer clinical practice guideline for patients at low or intermediate recurrence risk. Of the 12,292 patients treated with one of the recommended strategies, 1,993 were treated with expectant management (EM), 3,313 were treated with external beam radiotherapy (EBR), 567 were treated with brachytherapy (BT), 5,954 were treated with prostatectomy (RP), and 465 were treated with external beam radiotherapy plus brachytherapy (EBRwBT). The remaining 26,042 patients received some other type of treatment or a combination of the recommended treatments.

Of the 26,042 individuals not receiving one of the recommended treatment strategies, 633 (2.4%) died due to prostate cancer within five years of diagnosis. Of the 12,944 individuals treated with a recommended treatment strategy, 83 (0.7%) died due to prostate cancer within five years of diagnosis. Patients treated with a recommended treatment strategy and patients not treated with a recommended treatment strategy differed significantly ($p < 0.05$ for each comparison) in terms of geographic area (SEER registry), race (Table 4-6), urban/rural classification (Table 4-7), tumor grade (Table 4-8), tumor stage (Table 4-9), year of diagnosis (Table 4-10), age at diagnosis (72.0 for patients treated with a recommended treatment strategy and 74.9 for patients treated with a non-recommended treatment strategy), and Charlson comorbidity score (0.25 for

patients treated with a recommended treatment strategy and 0.37 for patients treated with a non-recommended treatment strategy).

As discussed in Chapter 3, the propensity score was used to control for differences between treatment groups on potential confounders. In order for a variable to be a confounder, the variable must be related to both the treatment received and the outcome of interest. Omnibus tests for differences between treatment strategies for the distributions of registry, race (Table 4-11), urban/rural classification versus rural area (Table 4-12), tumor grade (Table 4-13), tumor stage (Table 4-14), year of diagnosis (Table 4-15), age at diagnosis (Table 4-16), and Charlson comorbidity score (Table 4-16) by initial treatment strategy identified significant differences for each of the hypothesized confounders ($p < 0.05$ for each).

The sections below report the results of the Cox proportional hazard and cost regressions for each comparison of treatment pairs. The Cox proportional hazard model was not used for comparisons including brachytherapy or external beam radiotherapy with brachytherapy because there were no deaths due to prostate cancer within 5 years of diagnosis for patients receiving either treatment strategy. While the lack of deaths due to prostate cancer in patients treated with either brachytherapy or external beam radiotherapy with brachytherapy could lead to a temptation to consider these treatment strategies superior, any such temptation must be tempered by the fact that these treatment strategies had significantly fewer patients diagnosed prior to 1999 leading to less opportunity for those patients treated using brachytherapy or external beam radiotherapy with brachytherapy to be observed for at least 5 years. The study sample included 1,208, 2,675, and 5,228 patients diagnosed prior to 1999 initially managed with expectant

management, external beam radiotherapy, and prostatectomy, respectively. Meanwhile, the study sample included only 287 and 260 patients diagnosed prior to 1999 receiving brachytherapy and external beam radiotherapy with brachytherapy, respectively.

Expectant Management vs. External Beam Radiotherapy

The comparison of patients receiving expectant management and external beam radiotherapy included 1,993 patients initially managed using expectant management and 3,313 patients initially treated using external beam radiotherapy. Of the 1,993 patients treated using expectant management, 20 died due to prostate cancer within five years of diagnosis. The 5-year KM estimate of the prostate cancer-specific survival function for expectant management was 0.9872. Of the 3,313 patients treated using external beam radiotherapy, 37 died due to prostate cancer within five years of diagnosis. The 5-year KM estimate of the prostate cancer-specific survival function for external beam radiotherapy was 0.9874.

The hazard ratio comparing expectant management to external beam radiotherapy was 0.505 (95% confidence interval: 0.263 – 0.969), indicating patients treated with external beam radiotherapy were only 50.5% as likely to die due to prostate cancer at any time as patients treated with expectant management controlling for the hypothesized confounders (i.e., SEER registry, urban/rural classification, race, tumor grade, tumor stage, age at diagnosis, Charlson comorbidity score, and year of diagnosis) through inclusion of the propensity score in the Cox proportional hazards model. The assumption of proportional hazards seems reasonable based on inspection of the plot of the log cumulative hazard versus log time presented in Figure 4-1 (i.e., the curves are roughly parallel). Additionally, neither the interaction term for treatment and time ($p = 0.245$) nor the interaction term for the propensity score and time ($p = 0.449$) were significant. As

such, it is reasonable to use the Cox proportional hazard model to compare expectant management and external beam radiotherapy.

The cost of prostate cancer-specific health care use in the first five years following diagnosis was \$15,460 for patients initially treated with expectant management and \$19,060 for patients initially treated with external beam radiotherapy. The \$3,600 difference in 5-year cost was statistically significant (Wald statistic = 97.7, $p < 0.01$). Cumulative cost by initial treatment strategy for patients initially managed using expectant management or external beam radiotherapy is presented in Figure 4-2.

The minimum willingness-to-pay value to make treatment with external beam radiotherapy cost-effective compared to expectant management was \$600,000 per death due to prostate cancer prevented over the course of five years.

Expectant Management vs. Brachytherapy

The comparison of patients receiving expectant management and brachytherapy included 1,993 patients initially managed using expectant management and 567 patients initially treated using brachytherapy. Of the 1,993 patients treated using expectant management, 20 died due to prostate cancer within five years of diagnosis. The 5-year KM estimate of the prostate cancer-specific survival function for expectant management was 0.9872. Of the 567 patients treated using brachytherapy, none died due to prostate cancer within five years of diagnosis. The 5-year KM estimate of the prostate cancer-specific survival function for brachytherapy was 1.

The cost of prostate cancer-specific health care use in the first five years following diagnosis was \$15,780 for patients initially treated with expectant management and \$18,990 for patients initially treated with brachytherapy. The \$3,210 difference in 5-year cost was statistically significant (Wald statistic = 13.9, $p < 0.01$). Cumulative cost by

initial treatment strategy for patients initially managed using expectant management or brachytherapy is presented in Figure 4-3.

Expectant Management vs. Prostatectomy

The comparison of patients receiving expectant management and prostatectomy included 1,993 patients initially managed using expectant management and 5,954 patients initially treated using prostatectomy. Of the 1,993 patients treated using expectant management, 20 died due to prostate cancer within five years of diagnosis. The 5-year KM estimate of the prostate cancer-specific survival function for expectant management was 0.9872. Of the 5,954 patients treated using prostatectomy, 26 died due to prostate cancer within five years of diagnosis. The 5-year KM estimate of the prostate cancer-specific survival function for prostatectomy was 0.9955.

The hazard ratio comparing expectant management to prostatectomy was 0.307 (95% confidence interval: 0.137 – 0.690), indicating patients treated with prostatectomy were only 30.7% as likely to die due to prostate cancer at any time as patients treated with expectant management controlling for the hypothesized confounders through inclusion of the propensity score in the Cox proportional hazards model. The assumption of proportional hazards seems reasonable based on inspection of the plot of the log cumulative hazard versus log time presented in Figure 4-4 (i.e., the curves are roughly parallel). Additionally, neither the interaction term for treatment and time ($p = 0.199$) nor the interaction term for the propensity score and time ($p = 0.728$) were significant. As such, it is reasonable to use the Cox proportional hazard model to compare expectant management and prostatectomy.

The cost of prostate cancer-specific health care use in the first five years following diagnosis was \$15,640 for patients initially treated with expectant management and

\$21,460 for patients initially treated with prostatectomy. The \$5,820 difference in 5-year cost was statistically significant (Wald statistic = 158.1, $p < 0.01$). Cumulative cost by initial treatment strategy for patients initially managed using expectant management or prostatectomy is presented in Figure 4-5.

The minimum willingness-to-pay value to make treatment with prostatectomy cost-effective compared to expectant management was \$646,670 per death due to prostate cancer prevented over the course of five years.

Expectant Management vs. External Beam Radiotherapy with Brachytherapy

The comparison of patients receiving expectant management and external beam radiotherapy with brachytherapy included 1,993 patients initially managed using expectant management and 465 patients initially treated using external beam radiotherapy with brachytherapy. Of the 1,993 patients treated using expectant management, 20 died due to prostate cancer within five years of diagnosis. The 5-year KM estimate of the prostate cancer-specific survival function for expectant management was 0.9872. Of the 465 patients treated using external beam radiotherapy with brachytherapy, none died due to prostate cancer within five years of diagnosis. The 5-year KM estimate of the prostate cancer-specific survival function for patients initially treated using external beam radiotherapy with brachytherapy was 1.

The cost of prostate cancer-specific health care use in the first five years following diagnosis was \$14,970 for patients initially treated with expectant management and \$21,710 for patients initially treated using external beam radiotherapy with brachytherapy. The \$6,740 difference in 5-year cost was statistically significant (Wald statistic = 25.0, $p < 0.01$). Cumulative cost by initial treatment strategy for patients

initially managed using expectant management or external beam radiotherapy with brachytherapy is presented in Figure 4-6.

External Beam Radiotherapy vs. Brachytherapy

The comparison of patients receiving external beam radiotherapy and brachytherapy included 3,313 patients initially managed using external beam radiotherapy and 567 patients initially treated using brachytherapy. Of the 3,313 patients treated using external beam radiotherapy, 37 died due to prostate cancer within five years of diagnosis. The 5-year KM estimate of the prostate cancer-specific survival function for patients initially treated using external beam radiotherapy was 0.9874. Of the 567 patients treated using brachytherapy, none died due to prostate cancer within five years of diagnosis. The Kaplan-Meier (KM) estimate of the 5-year prostate cancer-specific survival function for patients initially treated with brachytherapy was 1.

The cost of prostate cancer-specific health care use in the first five years following diagnosis was \$17,890 for patients initially treated with external beam radiotherapy and \$17,260 for patients initially treated with brachytherapy. The \$630 difference in 5-year cost was statistically significant (Wald statistic = 8.1, $p < 0.01$). Cumulative cost by initial treatment strategy for patients initially managed using external beam radiotherapy or brachytherapy is presented in Figure 4-7.

External Beam Radiotherapy vs. Prostatectomy

The comparison of patients receiving external beam radiotherapy to those receiving prostatectomy included 3,313 patients initially managed using external beam radiotherapy and 5,954 patients initially treated using prostatectomy. Of the 3,313 patients treated using external beam radiotherapy, 37 died due to prostate cancer within five years of diagnosis. The 5-year KM estimate of the prostate cancer-specific survival

function for patients initially treated using external beam radiotherapy was 0.9874. Of the 5,954 patients treated using prostatectomy, 26 died due to prostate cancer within five years of diagnosis. For patients treated with prostatectomy the 5-year KM survival function estimate was 0.9955.

The hazard ratio comparing external beam radiotherapy to prostatectomy was 0.432 (95% confidence interval: 0.224 – 0.833), indicating patients treated with radical prostatectomy were only 43.2% as likely to die at any time as patients treated with external beam radiotherapy controlling for the hypothesized confounders through inclusion of the propensity score in the Cox proportional hazards model. The assumption of proportional hazards seems reasonable based on inspection of the plot of the log cumulative hazard versus log time presented in Figure 4-8 (i.e., the curves are roughly parallel). Additionally, the interaction term for propensity score and time ($p = 0.498$) was not significant. The interaction term for treatment and time ($p = 0.005$) was significant. The significant interaction between treatment and time could be an indication of a violation of the proportional hazards assumption. Despite the significant interaction between treatment and time, the parallel nature of the log cumulative hazard versus log time plot (Figure 4-8) provides sufficient support for the assumption of proportional hazards and supports the validity of using the Cox proportional hazards model to compare external beam radiotherapy and prostatectomy.

The cost of prostate cancer-specific health care use in the first five years following diagnosis was \$20,190 for patients initially treated with external beam radiotherapy and \$23,460 for patients initially treated with prostatectomy. The \$3,260 difference in 5-year cost was statistically significant (Wald statistic = 91.8, $p < 0.01$). Cumulative cost by

initial treatment strategy for patients initially managed using external beam radiotherapy or prostatectomy is presented in Figure 4-9.

The minimum willingness-to-pay value to make treatment with prostatectomy cost-effective compared to external beam radiotherapy was \$465,710 per death due to prostate cancer prevented over the course of five years.

External Beam Radiotherapy vs. External Beam Radiotherapy with Brachytherapy

The comparison of patients receiving external beam radiotherapy and external beam radiotherapy with brachytherapy included 3,313 patients initially managed using external beam radiotherapy and 465 patients initially treated using external beam radiotherapy with brachytherapy. Of the 3,313 patients treated using external beam radiotherapy, 37 died due to prostate cancer within five years of diagnosis. The 5-year KM estimate of the prostate cancer-specific survival function for patients initially treated using external beam radiotherapy was 0.9874. Of the 465 patients treated using external beam radiotherapy with brachytherapy, none died due to prostate cancer within five years of diagnosis. The 5-year KM estimate of the prostate cancer-specific survival function for patients initially treated using external beam radiotherapy with brachytherapy was 1.

The cost of prostate cancer-specific health care use in the first five years following diagnosis was \$17,730 for patients initially treated with external beam radiotherapy and \$20,400 for patients initially treated using external beam radiotherapy with brachytherapy. The \$2,680 difference in 5-year cost was statistically significant (Wald statistic = 34.9, $p < 0.01$). Cumulative cost by initial treatment strategy for patients initially managed using external beam radiotherapy or external beam radiotherapy with brachytherapy is presented in Figure 4-10.

Brachytherapy vs. Prostatectomy

The comparison of patients receiving brachytherapy and prostatectomy included 567 patients initially managed using brachytherapy and 5,954 patients initially treated using prostatectomy. Of the 567 patients treated using brachytherapy, none died due to prostate cancer within five years of diagnosis. The 5-year KM estimate of the prostate cancer-specific survival function for brachytherapy was 1. Of the 5,954 patients treated using prostatectomy, 26 died due to prostate cancer within five years of diagnosis. The 5-year KM estimate of the prostate cancer-specific survival function for prostatectomy was 0.9955.

The cost of prostate cancer-specific health care use in the first five years following diagnosis was \$18,430 for patients initially treated with brachytherapy and \$17,100 for patients initially treated using prostatectomy. The \$1,340 difference in 5-year cost was statistically significant (Wald statistic = 33.5, $p < 0.01$). Cumulative cost by initial treatment strategy for patients initially managed using brachytherapy or prostatectomy is presented in Figure 4-11.

Brachytherapy vs. External Beam Radiotherapy with Brachytherapy

The comparison of patients receiving brachytherapy and those patients receiving external beam radiotherapy with brachytherapy included 567 patients initially managed using brachytherapy and 465 patients initially treated using external beam radiotherapy with brachytherapy. Of the 567 patients treated using brachytherapy, none died due to prostate cancer within five years of diagnosis. The 5-year KM estimate of the prostate cancer-specific survival function for brachytherapy was 1. Of the 465 patients treated using external beam radiotherapy with brachytherapy, none died due to prostate cancer within five years of diagnosis. The 5-year Kaplan-Meier estimate of the prostate cancer-

specific survival function for treatment using external beam radiotherapy with brachytherapy was 1.

The cost of prostate cancer-specific health care use in the first five years following diagnosis was \$18,380 for patients initially treated with brachytherapy and \$22,160 for patients initially treated using external beam radiotherapy with brachytherapy. The \$3,780 difference in 5-year cost was statistically significant (Wald statistic = 6.07, $p < 0.01$). Cumulative cost by initial treatment strategy for patients initially managed using brachytherapy or external beam radiotherapy with brachytherapy is presented in Figure 4-12.

Prostatectomy vs. External Beam Radiotherapy with Brachytherapy

The comparison of patients receiving prostatectomy and external beam radiotherapy with brachytherapy included 5,954 patients initially managed using prostatectomy and 465 patients initially treated using external beam radiotherapy with brachytherapy. Of the 5,954 patients treated using prostatectomy, 26 died due to prostate cancer within five years of diagnosis. The 5-year KM estimate of the prostate cancer-specific survival function for prostatectomy was 0.9955. Of the 465 patients treated using external beam radiotherapy with brachytherapy, none died due to prostate cancer within five years of diagnosis. The 5-year KM estimate of the prostate cancer-specific survival function for treatment using external beam radiotherapy with brachytherapy was 1.

The cost of prostate cancer-specific health care use in the first 5 years following diagnosis was \$17,720 for patients initially treated with prostatectomy and \$20,330 for patients initially treated using external beam radiotherapy with brachytherapy. The \$2,600 difference in 4-year cost was statistically significant (Wald statistic = 56.9, $p <$

0.01). Cumulative cost by initial treatment strategy for patients initially managed using prostatectomy or external beam radiotherapy with brachytherapy is presented in Figure 4-13.

Table 4-1. Race distribution by 5-year prostate cancer-specific survival status

	Patients with prostate cancer-specific death within 5 years (%)	Patients without prostate cancer-specific death within 5 years (%)
White	85.8	82.7
Black	8.4	12.2
Asian	2.6	1.7
Hispanic	1.5	1.1
Native North American	0.2	0.4
Other/unknown	1.6	2.0

Table 4-2. Urban/rural classification distribution by 5-year prostate cancer-specific survival status

	Patients with prostate cancer-specific death within 5 years (%)	Patients without prostate cancer-specific death within 5 years (%)
Big metro	61.1	52.0
Metro	21.0	25.7
Urban	7.2	11.5
Less urban	9.0	9.6
Rural	1.8	1.3

Table 4-3. Tumor grade distribution by 5-year prostate cancer-specific survival status

	Patients with prostate cancer-specific death within 5 years (%)	Patients without prostate cancer-specific death within 5 years (%)
Well differentiated	19.6	14.4
Moderately differentiated	80.4	85.6

Table 4-4. Tumor stage distribution by 5-year prostate cancer-specific survival status

	Patients with prostate cancer-specific death within 5 years (%)	Patients without prostate cancer-specific death within 5 years (%)
Clinically unapparent	37.2	26.4
Clinically/ radiographically apparent	33.2	36.3
Clinically unapparent or clinically/ radiographically apparent	29.6	37.3

Table 4-5. Diagnosis year by 5-year prostate cancer-specific survival status

	Patients with prostate cancer-specific death within 5 years (%)	Patients without prostate cancer-specific death within 5 years (%)
1992	97.2	2.8
1993	97.2	2.8
1994	97.5	2.5
1995	97.7	2.3
1996	98.0	2.0
1997	98.9	1.1
1998	99.2	0.8
1999	99.7	0.3

Table 4-6. Race distribution for patients treated with recommended and non-recommended strategies

	Recommended treatment strategy (%)	Non-recommended treatment strategy (%)
White	85.8	85.4
Black	8.0	9.5
Asian	2.7	2.1
Hispanic	1.5	1.6
Native North American	0.2	0.2
Other/unknown	1.8	1.2

Table 4-7. Urban/rural classification distribution for patients treated with recommended and non-recommended strategies

	Recommended treatment strategy (%)	Non-recommended treatment strategy (%)
Big metro	58.0	67.3
Metro	23.2	16.5
Urban	7.5	6.6
Less urban	9.5	8.0
Rural	1.8	1.6

Table 4-8. Tumor grade distribution for patients treated with recommended and non-recommended strategies

	Recommended treatment strategy (%)	Non-recommended treatment strategy (%)
Well differentiated	23.0	12.2
Moderately differentiated	77.0	87.8

Table 4-9. Tumor stage distribution for patients treated with recommended and non-recommended strategies

	Recommended treatment strategy (%)	Non-recommended treatment strategy (%)
Clinically unapparent	38.8	33.4
Clinically or radiographically apparent	31.9	36.0
Clinically unapparent or clinically or radiographically apparent	29.4	30.6

Table 4-10. Diagnosis year distribution for patients treated with recommended and non-recommended strategies

	Recommended treatment strategy (%)	Non-recommended treatment strategy (%)
1992	29.3	70.7
1993	25.9	74.1
1994	26.2	73.8
1995	26.5	73.5
1996	25.2	74.8
1997	25.1	74.9
1998	53.3	46.7
1999	51.2	48.8

Table 4-11. Race distribution by initial treatment strategy

	EM (%)	EBR (%)	BT (%)	RP (%)	EBRw/BT (%)
White	82.0	80.2	89.1	89.0	86.9
Black	11.9	16.1	6.5	5.4	9.0
Asian	2.8	1.7	1.4	2.2	2.2
Hispanic	1.8	0.9	1.6	2.0	1.3
Native North American	0.2	0.1	0.2	0.2	0.0
Other/unknown	1.3	1.1	1.2	1.3	0.6

Table 4-12. Urban/rural classification distribution by initial treatment strategy

	EM (%)	EBR (%)	BT (%)	RP (%)	EBRw/BT (%)
Big metro	65.1	80.1	69.5	59.7	79.8
Metro	14.4	10.6	17.3	20.8	11.2
Urban	8.8	4.0	4.2	7.8	4.1
Less urban	10.2	4.4	8.3	9.6	3.9
Rural	1.5	0.9	0.7	2.1	1.1

Table 4-13. Tumor grade distribution by initial treatment strategy

	EM (%)	EBR (%)	BT (%)	RP (%)	EBRw/BT (%)
Well differentiated	19.3	12.7	7.9	10.4	7.7
Moderately differentiated	80.7	87.3	92.1	89.6	92.3

Table 4-14. Tumor stage distribution by initial treatment strategy

	EM (%)	EBR (%)	BT (%)	RP (%)	EBRw/BT (%)
Clinically unapparent	36.6	32.0	42.3	32.2	34.4
Clinically/radiographically apparent confined to prostate	26.4	36.8	28.2	39.8	33.1
Clinically unapparent or clinically/radiographically apparent confined to prostate	37.0	31.2	29.5	28.1	32.5

Table 4-15. Diagnosis year distribution by initial treatment strategy

	EM (%)	EBR (%)	BT (%)	RP (%)	EBRw/BT (%)
1992	2.9	27.5	0.2	69.4	0.1
1993	3.8	30.7	0.4	64.9	0.2
1994	4.9	28.5	0.6	65.2	0.8
1995	6.7	25.3	0.8	66.3	0.8
1996	8.4	23.5	2.5	64.7	1.0
1997	8.5	20.3	2.8	65.3	3.1
1998	31.0	26.0	8.0	27.6	7.5
1999	29.8	24.2	10.6	27.6	7.8

Table 4-16. Age and Charlson comorbidity score by initial treatment strategy

	EM Mean (sd)	EBR Mean (sd)	BT Mean (sd)	RP Mean (sd)	EBRw/BT Mean (sd)
Age at diagnosis	76.0 y (5.7)	73.4 y (4.3)	72.0 y (3.9)	69.9 y (3.2)	72.3 y (4.0)
Charlson comorbidity score	0.382 (0.796)	0.334 (0.686)	0.252 (0.636)	0.164 (0.485)	0.217 (0.551)

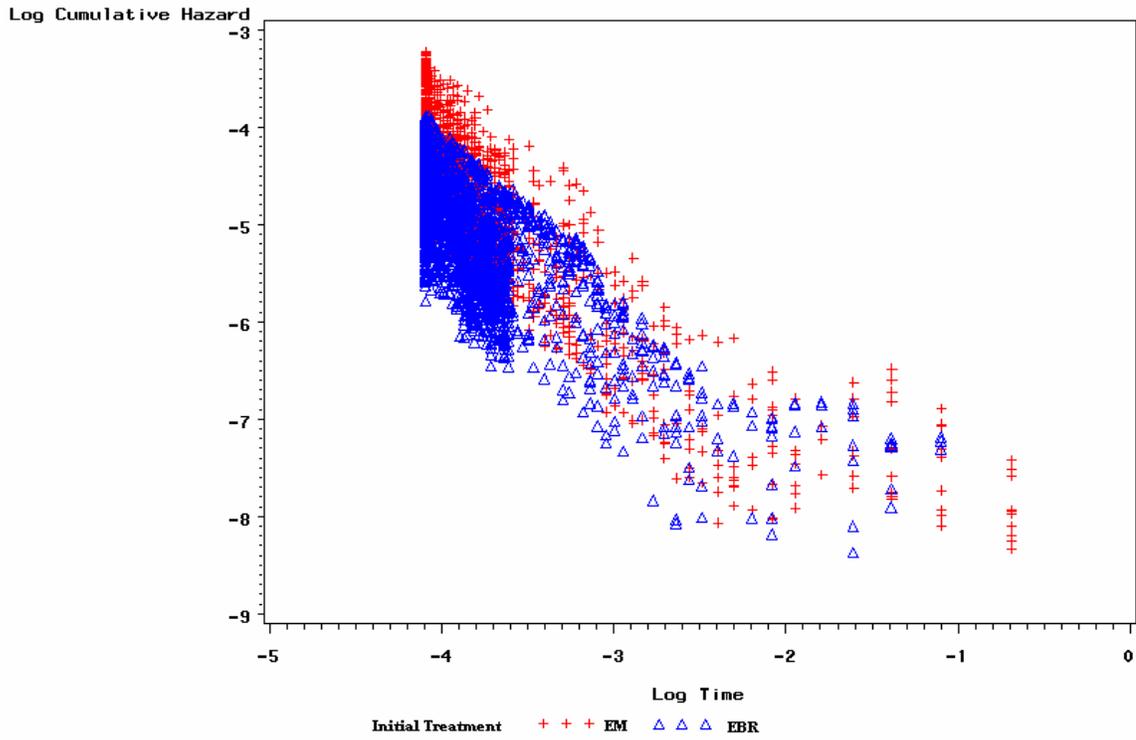


Figure 4-1. Expectant management (EM) vs. external beam radiotherapy (EBR) log cumulative hazard vs. log time

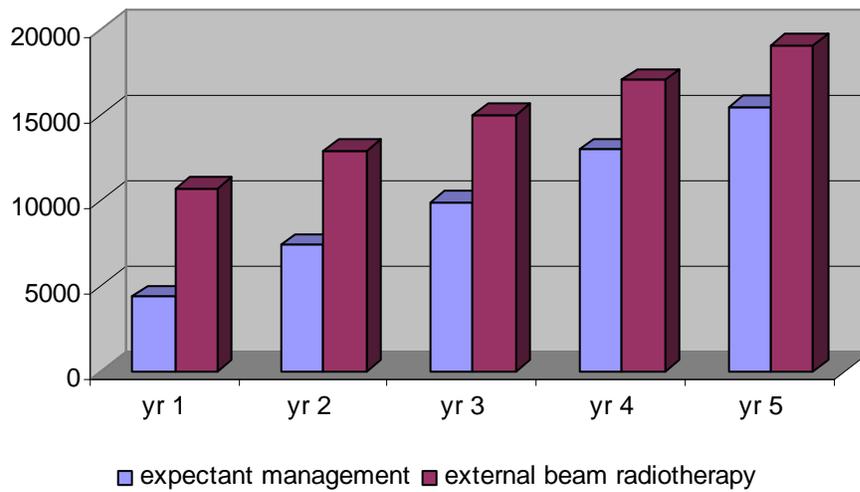


Figure 4-2. Expectant management vs. external beam radiotherapy cumulative cost by year

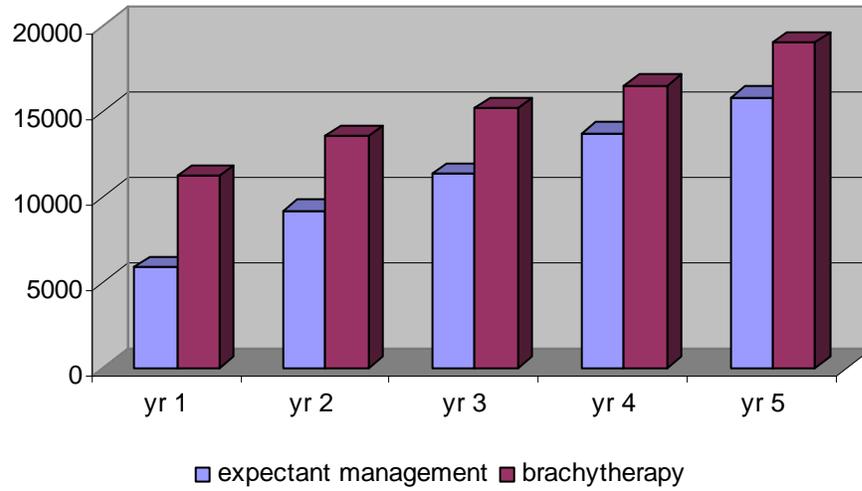


Figure 4-3. Expectant management vs. brachytherapy cumulative cost by year

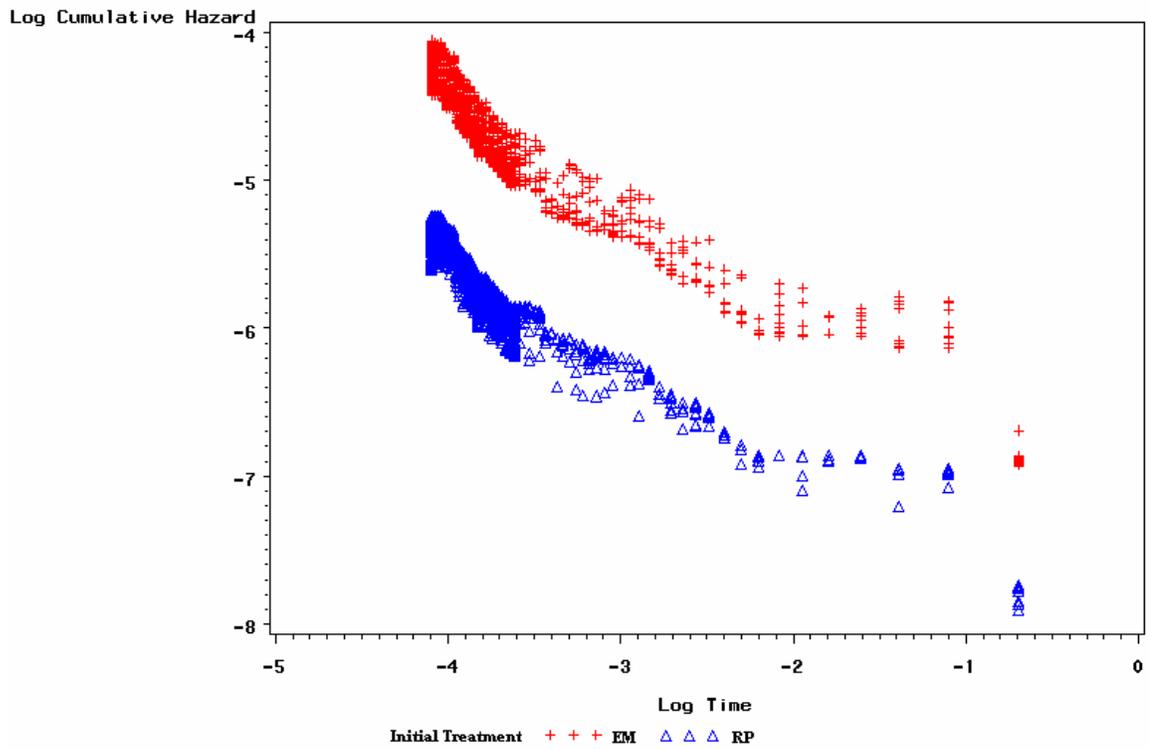


Figure 4-4. Expectant management (EM) vs. prostatectomy (RP) log cumulative hazard vs. log time

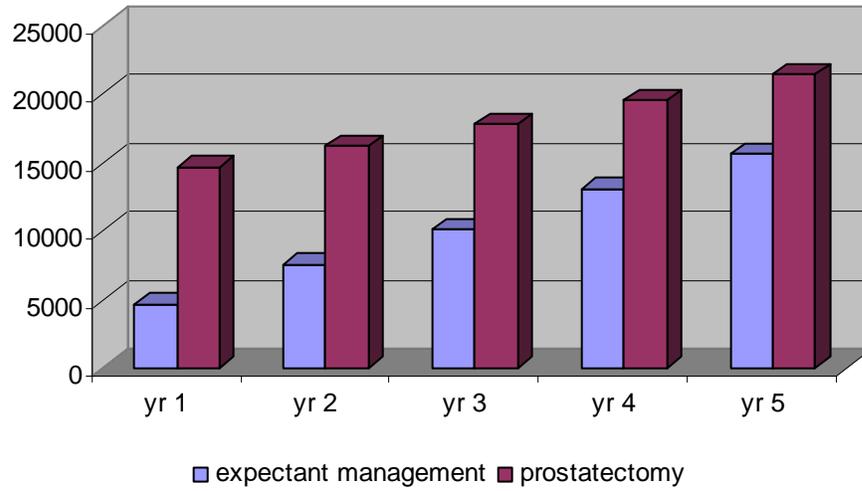


Figure 4-5. Expectant management vs. prostatectomy cumulative cost by year

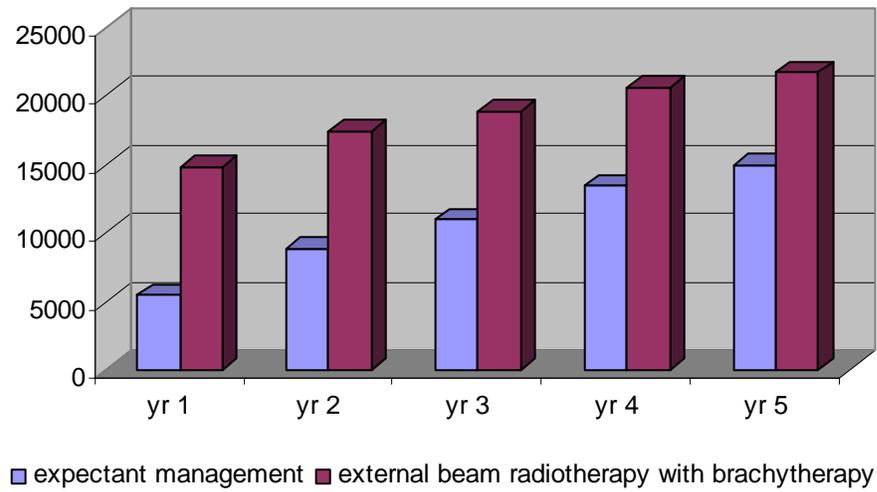


Figure 4-6. Expectant management vs. external beam radiotherapy with brachytherapy cumulative cost by year

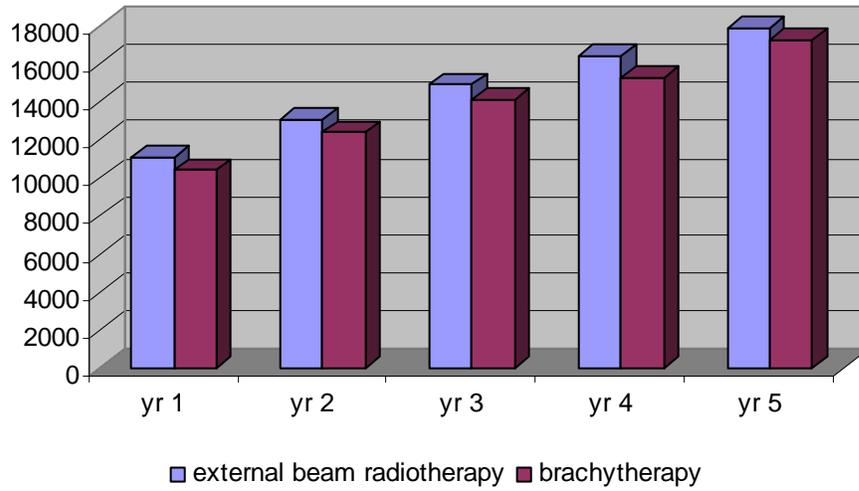


Figure 4-7. External beam radiotherapy vs. brachytherapy cumulative cost by year

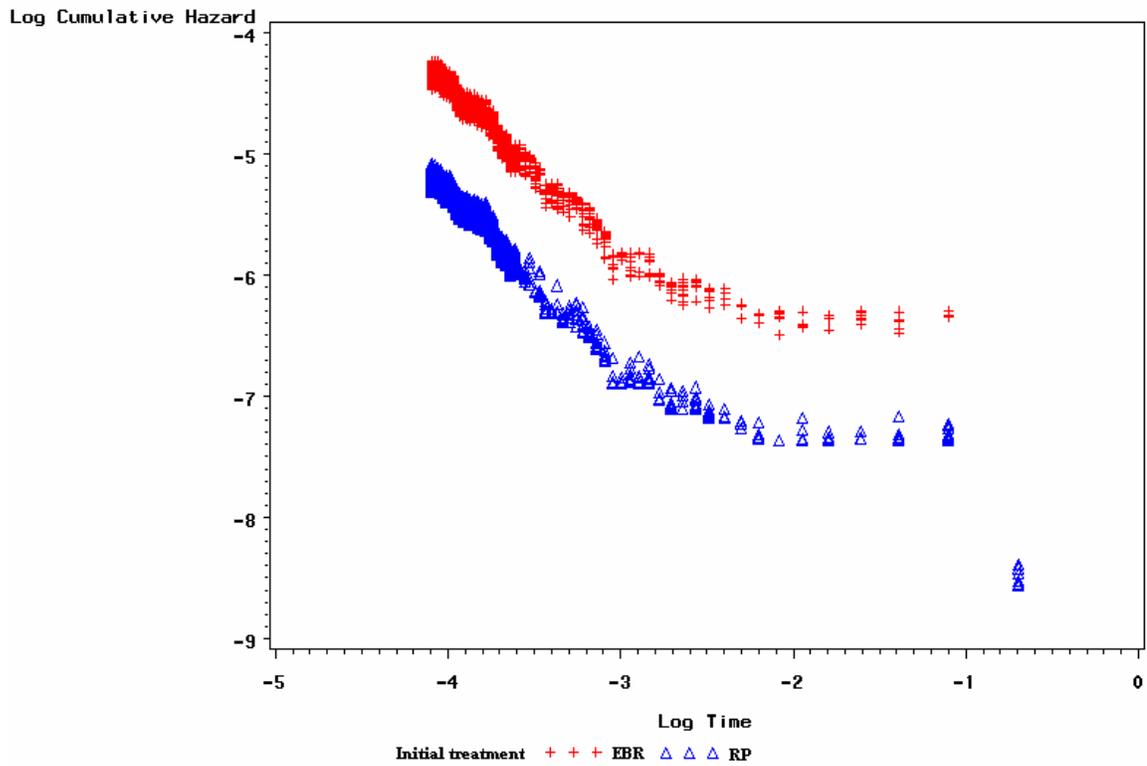


Figure 4-8. External beam radiotherapy (EBR) vs. prostatectomy (RP) log cumulative hazard vs. log time

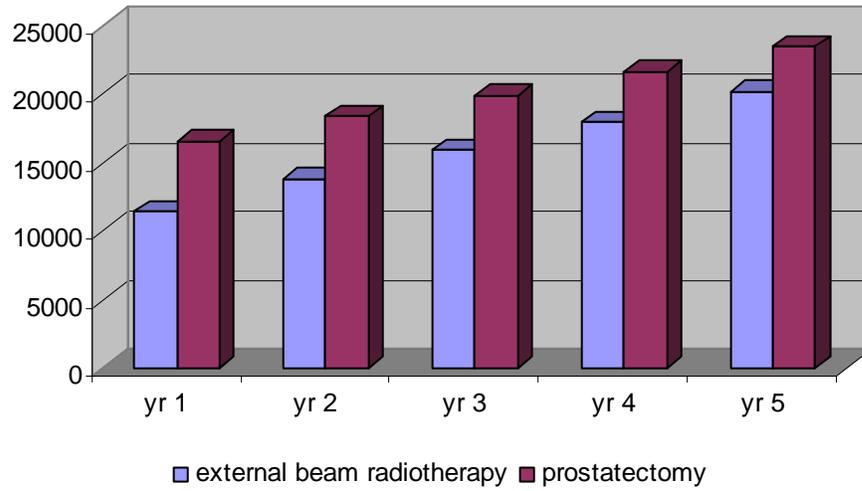


Figure 4-9. External beam radiotherapy vs. prostatectomy cumulative cost by year

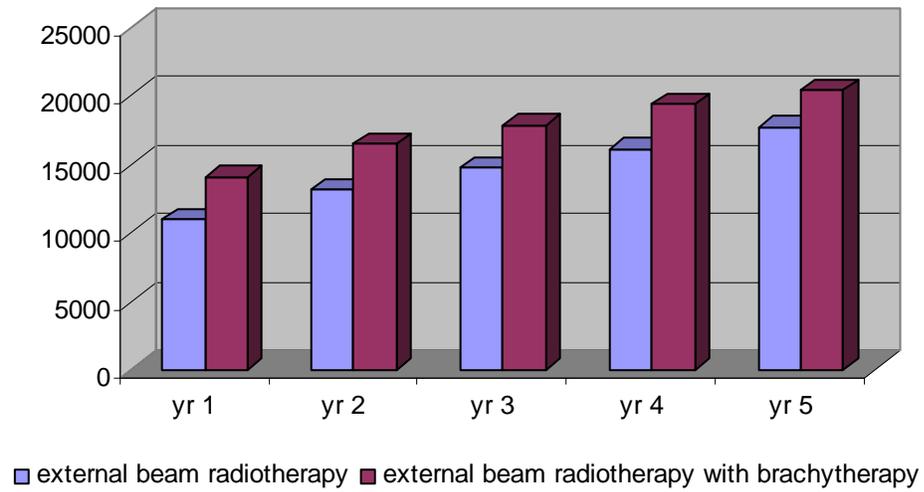


Figure 4-10. External beam radiotherapy vs. external beam radiotherapy with brachytherapy cumulative cost by year

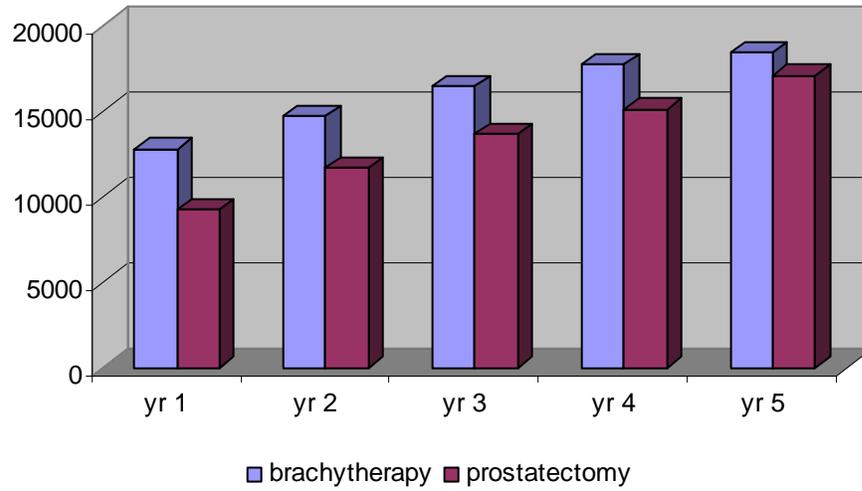


Figure 4-11. Brachytherapy vs. prostatectomy cumulative cost by year

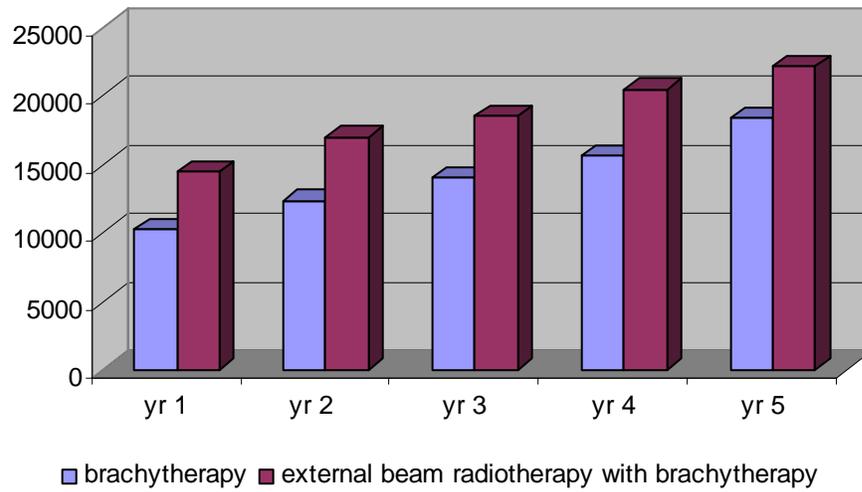


Figure 4-12. Brachytherapy vs. external beam radiotherapy with brachytherapy cumulative cost by year

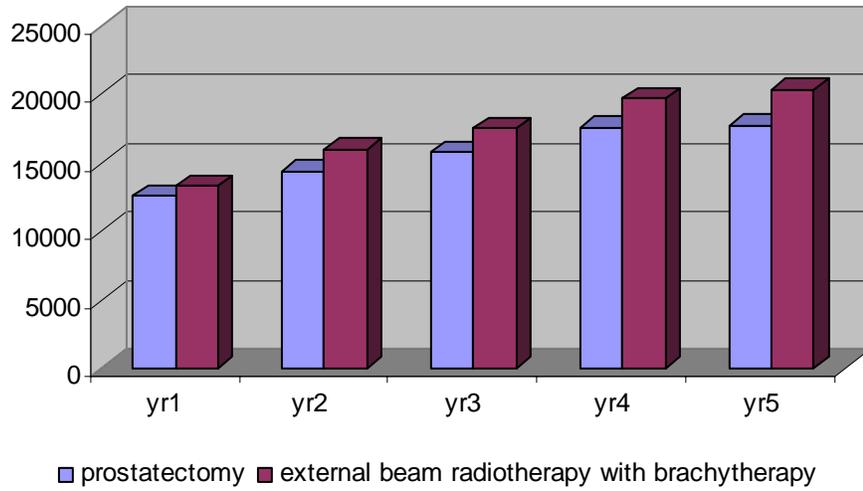


Figure 4-13. Prostatectomy vs. external beam radiotherapy with brachytherapy cumulative cost by year

CHAPTER 5 DISCUSSION

Limitations

Our study has several significant limitations. First, the limited number of patients initially treated using either brachytherapy or external beam radiotherapy with brachytherapy prevented us from being able to compare the clinical effectiveness of treatment using either brachytherapy or external beam radiotherapy with brachytherapy to the clinical effectiveness of any of the other recommended treatment strategies. However, it was possible to compare treatment using brachytherapy or external beam radiotherapy with brachytherapy to all other recommended treatment strategies in terms of the 5-year cost of prostate cancer-specific healthcare use.

Second, the findings of our study must be interpreted in light of the study's observation design. Given the lack of randomization, the potential exists for any differences in the effectiveness or cost of the treatments to be the result of a selection bias leading to non-equivalent groups rather than a true difference in the effectiveness or cost of the treatments being compared. Indeed, comparison of treatment groups for differences in SEER registry (an indicator of geographic area), urban/rural classification, race, tumor stage, tumor grade, year of diagnosis, age at diagnosis, and Charlson comorbidity score found significant differences for each between the treatment groups. Furthermore, each of these characteristics (except the Charlson comorbidity score) was related to prostate cancer-specific death. Despite the presence of a selection bias, confidence in our results is strengthened by the use of a multivariate analysis

incorporating the calculated propensity score, which controls for differences between treatments in the previously listed characteristics related to the treatment strategy a patient received, to compare prostate cancer-specific mortality and 5-year cost of prostate cancer-specific healthcare.

While the use of an observational study design is a limitation, it is also a strength of our study because it allows for the assessment of whether differences in effectiveness exist between the compared treatments as opposed to a difference in efficacy. Additionally, the observational design provides a more realistic estimate of the cost of treatment because an experimental design typically influences the pattern of care through the experiment's protocol requirements (e.g., additional follow-up visits and tests). Information on effectiveness and costs in a non-protocol-driven environment can be very useful seeing as most individuals are not treated in the clinical trial setting. Instead, most individuals are treated in the real world setting with all of its potential effect modifiers and without protocol-driven follow-up requirements.

Classification of the cause of death was based on the death certificate-coded cause of death. It is possible that relying on the inaccurate coding of the cause of death on the death certificated resulted in some patients classified in our study as dying due to prostate cancer having instead died due to some other cause. Similarly, it is possible that some patients treated as censored observations in our study did indeed die due to prostate cancer but the death certificate did not reflect prostate cancer as the cause of death.

In terms of the estimation of the cost of prostate cancer-specific healthcare use, we relied upon ICD9-CM diagnosis codes on claims submitted to Medicare to determine if the claim was related to prostate cancer. It is possible that reliance upon billing diagnosis

codes caused us to classify some non-prostate cancer-related costs as related to prostate cancer. Additionally, the reliance upon billing diagnosis codes could have resulted in us classifying some prostate cancer-related costs as not being related to prostate cancer. Furthermore, our study was not able to account for the cost of prostate cancer-related healthcare (e.g., oral prescription medications) that is not covered by Medicare.

Prostate Cancer-Specific Mortality

We identified four studies published in the last ten years comparing the rate of prostate-cancer specific mortality between two or more of the treatment strategies recommended in the National Comprehensive Cancer Network prostate cancer clinical practice guideline. Similar to our study, two of the published studies examined 5-year prostate cancer-specific mortality. Our study found the 5-year prostate cancer-specific mortality rate for patients treated with expectant management, external beam radiotherapy, brachytherapy, prostatectomy, and external beam radiotherapy with brachytherapy to be 1.3%, 1.3%, 0%, 0.4%, and 0% respectively. However, as noted in Chapter 4, the rates for brachytherapy and external beam radiotherapy with brachytherapy must be interpreted with caution due to the relatively small number of patients with the potential for five years of follow-up receiving brachytherapy or external beam radiotherapy with brachytherapy.

Holmberg et al. (18) found the 5-year prostate cancer-specific mortality rate for patients treated with expectant management (EM) or prostatectomy (RP) to be 4.6% and 2.6% respectively in a prospective randomized trial with a hazard ratio of 0.45 (95% CI: 0.25- 0.84) favoring prostatectomy. The hazard ratio in our study also favored prostatectomy (HR = 0.307, 95% CI: 0.137 – 0.690). Differences in survival rates between the study by Holmberg et al. and our study (EM: 4.6% vs. 1.3%; RP: 2.6% vs.

0.4%) are likely due to patients included in our study having tumors of a less advanced stage.

Fowler et al. (7) found the 5-year prostate cancer-specific mortality rate for patients treated with radical prostatectomy or external beam radiotherapy (EBR) to be 5% and 11%, respectively. Fowler et al. did not report a hazard ratio, but stated the difference in prostate cancer-specific survival was not significant. Our study did find a significant difference in survival (HR = 0.66, 95% CI: 0.47-0.91). Differences in survival rates between the study by Fowler et al. and our study (RP: 5.0% vs. 0.4%; EBR: 11.0% vs. 1.3%) are likely due to patients included in our study having less advanced tumors in terms of both stage and grade than patients in the study by Fowler and colleagues.

Prostate Cancer-Specific Cost

Our study significantly bolsters the available information on the cost of treating prostate cancer. As noted in Chapter 2, seven studies published since 1995 have addressed prostate cancer treatment-specific costs. The only study examining costs beyond the initial treatment period was carried out by Perez et al. (32) and used a modeling approach to estimate the accrual of cost for five years beyond the initial treatment phase. Our study has provided 5-year prostate cancer-specific healthcare use cost estimates for treatment strategies recommended in the National Comprehensive Cancer Network prostate cancer clinical practice guideline for patients with localized prostate cancer (i.e. patients at either low or intermediate risk of prostate cancer recurrence). Each estimate was obtained using patient-level data. As such, the cost data was stochastic in nature, which allowed for the testing of differences in cost between treatments using inferential statistics. Our study appears to be the first study of prostate cancer-specific health care cost to properly account for censoring of cost data.

The wide range of the cost estimates for the same treatment strategy obtained when comparing a specific treatment to each of the other recommended treatments is slightly surprising. For example, there is a difference of \$6,360 between estimates of the 5-year cost of prostatectomy depending on whether the estimate was made in the comparison with brachytherapy or external beam radiotherapy. The cost of prostatectomy was \$17,100 when compared to brachytherapy, and the cost of prostatectomy was \$23,460 when compared to external beam radiotherapy. The range of the cost estimates for the other treatment strategies were not as dramatic. The ranges for expectant management, external beam radiotherapy, brachytherapy, and external beam radiotherapy with brachytherapy were \$810, \$2,460, \$1,730, and \$1,830, respectively.

The likely explanation for the differences in the cost estimates for the same treatment is the difference in the values of the variables included in the propensity score (SEER registry, urban/rural classification, tumor stage, etc.) between a patient equally likely to receive expectant management or prostatectomy (i.e., a patient with a set of values for the variables in the propensity score resulting in the propensity score calculated in the expectant management versus prostatectomy comparison equaling 0.5) and a patient equally likely to receive external beam radiotherapy or prostatectomy (i.e., a patient with a set of values for the variables in the propensity score resulting in the propensity score calculated in the external beam radiotherapy versus prostatectomy comparison equaling 0.5). A wide range of the cost estimates for the same treatment is expected in light of the realization that each estimate is for a specific set of values for the variables included in the propensity score. As such, conclusions about the cost of treatments estimated using the methods of our study should be limited to relative

differences in cost between treatment strategies rather than the provision of an estimate to be used for the purposes of estimating the absolute cost of providing care using a specific treatment. An absolute estimate of the cost of a treatment would depend on the type of patient (geographic location, urban/rural classification, tumor stage, tumor grade, etc.) for whom the estimate is desired.

Six studies published within the last ten years compare the cost of prostate cancer-specific healthcare use. The study conducted by Perez et al. (32) was the only study to examine cost beyond one year. However, in contrast to our study, the estimates by Perez et al. for costs beyond the initial treatment phase were based on a model developed using data from the literature rather than patient-level data. Therefore, Perez et al. were not able to test whether the difference in 5-year cost was statistically significant. Perez et al. found the 5-year cost of an initial treatment strategy using prostatectomy to be \$140 to \$1,230 less than treatment with external beam radiotherapy. Our study also found prostatectomy to be more expensive, but the cost differential identified in our study was larger (\$3260).

While our study focused on 5-year costs, some comparisons to the five studies published within the last ten years examining differences in the first year cost of prostate cancer treatment strategies can be made. Both our study and the study by Penson et al. (31) found the first year cost of prostatectomy to be greater than expectant management. Penson et al. found prostatectomy \$6,840 more than expectant management, and we found prostatectomy to cost an additional \$10,020. Penson et al. found external beam radiotherapy to be \$6,950 more than expectant management. Similarly, we found

treatment with external beam radiotherapy to be \$6,360 more than treatment with expectant management.

Comparing external beam radiotherapy to brachytherapy, Brandeis et al. (29) found a non-significant \$640 difference. We found external beam radiotherapy cost \$640 more than brachytherapy, but we did not test whether the difference was statistically significant. Though not statistically significant, external beam radiotherapy was also the more expensive treatment in the study by Brandeis and colleagues.

In the same study, Brandeis et al. (29) found external beam radiotherapy with brachytherapy to be \$9,110 more than brachytherapy. Our study also found external beam radiotherapy with brachytherapy to be more expensive than brachytherapy but by a smaller amount (\$4,180). Comparing external beam radiotherapy with brachytherapy to prostatectomy, Brandeis et al. found external beam radiotherapy with brachytherapy to be \$5,390 more expensive while our study again found a smaller difference (\$750). Comparing external beam radiotherapy with brachytherapy to external beam radiotherapy, Brandeis et al. found external beam radiotherapy with brachytherapy to be \$8,470 more than external beam radiotherapy. Again, we found a similar but smaller difference (\$3,160).

Three of the previously published studies compared the cost of external beam radiotherapy to that of prostatectomy. Burkardt et al. (30) and Brandeis et al. (29) found prostatectomy to be more expensive by \$3710 and \$3080, respectively. Our study found prostatectomy to be \$5,150 more than external beam radiotherapy. Penson et al. (31) did not find a difference in the cost of prostatectomy and external beam radiotherapy.

Three of the previously published studies also compared the cost of brachytherapy and prostatectomy. Similar to our study in which brachytherapy was \$3,560 more than prostatectomy, Wagner et al. (33) found brachytherapy to be more expensive than prostatectomy but by a smaller amount (\$5,930). In contrast, Brandeis et al. (29) found prostatectomy to cost \$3,720 more than brachytherapy. Kohan et al. (35) failed to find a difference in the cost of prostatectomy and brachytherapy.

Conclusions

Our study identified a number of differences in the treatments recommended in the NCCN prostate cancer clinical practice guideline. First, statistically significant differences in the 5-year cost of prostate cancer-specific healthcare were found in each comparison of recommended treatments. The differences in 5-year cost ranged between \$630 (comparing external beam radiotherapy to brachytherapy) and \$6740 (comparing external beam radiotherapy with brachytherapy to expectant management). The final determination of the degree to which these differences in cost are meaningful is left to the reader. In terms of clinical effectiveness, the findings regarding differences in the risk of death due to prostate cancer comparing external beam radiotherapy to expectant management, prostatectomy to expectant management, and prostatectomy to external beam radiotherapy are significant contributions to the literature. However, one must consider the fact that the absolute differences in survival were small when evaluating the clinical significance of the statistically significant differences in prostate cancer-specific mortality between the treatments. Finally, we provided valuable information regarding the cost of preventing one death due to prostate cancer over a 5-year time period associated with the use of external beam radiotherapy rather than expectant management

(\$600,000), prostatectomy rather than expectant management (\$646,670), and prostatectomy rather than external beam radiotherapy (\$465,710).

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BIOGRAPHICAL SKETCH

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