BASELINE HEALTH RELATED QUALITY OF LIFE AS CONFOUNDER IN OBSERVATIONAL RESEARCH FOR ELDERLY MEN WITH LOCALIZED PROSTATE CANCER

By

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To my beloved family

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LIST OF ABBREVIATIONS

BB	Bowel bother
BF	Bowel function
BP	Bodily pain
CaPSURE	Cancer of Prostate Strategic Urologic Research Endeavor
CGA	Comprehensive geriatric assessment
CI	Confidence interval
CT	Conservative treatment
DT	Definitive treatment
EM	Expectant management
GH	General health
HS	High school
HT	Hormonal therapy
IPCW	Inverse probability of censoring weighting
IPTW	Inverse probability of treatment weighting
IQR	Interquartile range
KPS	Karnofsky performance score
MH	Mental health
NCCN	National Comprehensive Cancer Network
PCI	UCLA prostate cancer index
PF	Physical functioning
PS	Propensity score
RE	Role-emotional
RO	Role-physical
RP	Radical prostatectomy

RT	Radiation therapy
SB	Sexual bother
SC	Some college
SD	Standard deviation
SF	Sexual function
SF-36	Medical outcome short form 36
SO	Social functioning
UB	Urinary bother
UF	Urinary function
VT	Vitality

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Prostate cancer is the most concerning non-skin malignancy in elderly men. Most prostate cancers are diagnosed at a localized stage. Definitive treatment includes radical prostatectomy and radiation therapy. Conservative treatment includes expectant management and hormonal therapy. Patient overall health status is a key consideration in treatment planning. Selection of relatively healthy patients to receive definitive treatment results in strong confounding in observational study regarding the treatment effectiveness.

Health related quality of life (HRQOL) measures multiple health dimensions. We conducted a cross-sectional study to examine the associations between a comprehensive range of baseline HRQOL variables and primary treatment selection in elderly men diagnosed with localized prostate cancer. The primary data source was the Cancer of Prostate Strategic Urologic Research Endeavor (CaPSURE). Three types of HRQOL were included, which were Karnofsky performance score, Medical Outcome Short-Form 36, and UCLA Prostate Cancer Index. Radical prostatectomy was found to be strongly associated with higher scores for all the HRQOL variables than the other primary treatments. Radiation therapy was moderately associated with higher HRQOL scores than both of the conservative treatments. The differences between

expectant management and hormonal therapy were minor. Several HRQOL variables, particularly those related to physical functioning, remained associated with definitive treatment, after controlling for the baseline sociodemographic, cancer characteristic and clinical factors.

We further investigated the confounding effect of the baseline HRQOL in elderly men diagnosed with low- or intermediate-risk prostate cancer. Both of the propensity score and weighting methods were used to control confounding. Radical prostatectomy and radiation therapy were found to be strongly associated with lower all-cause mortality than conservative treatment, after adjusting for commonly considered confounders. The associations were attenuated, but remained pronounced, after additional adjustment for the baseline HRQOL variables. Further analyses showed that the survival benefit was largely due to an implausibly lower risk of death from causes other than prostate cancer, indicating the persistence of substantial residual confounding. Additional adjustment for the baseline HRQOL variables is desirable, but insufficient, to rule out confounding bias. Randomized trial is warranted to evaluate the efficacy of primary treatment for localized prostate cancer.

CHAPTER 1
INTRODUCTION

Background

Prostate cancer has the highest incidence rate and the second highest death rate of all cancer types for American men. About 63% of all prostate cancer cases are diagnosed at age of 65 years old or above. More than 90% prostate cancers are diagnosed at the clinically localized stage.[1] Radical prostatectomy and radiation therapy are guideline recommended definitive treatments for clinically localized prostate cancer.[2] Because of the indolent nature of localized prostate cancer, patients are unlikely to benefit from definitive treatment when their life expectancies are predicted to be greater than 10 years from diagnosis, and conservative treatment is considered more appropriate. Expectant management is a guideline recommended conservative treatment, by which patients are closely monitored and definitive treatment is withheld until disease progresses aggressively.[2,3] Hormonal therapy is another conservative treatment. Although not recommended in current guidelines, it has been used in practice for palliative purpose in symptomatic patients whose life expectancy is too short to benefit from definitive treatment. Because uncertainties in life expectancy estimation increase dramatically with age, the treatment decision is more difficult to make for elderly patients than young patients.[3]

Health related quality of life (HRQOL) is a broad health concept incorporating multiple physical and psychosociological dimensions. These health dimensions are important prognostic factors for survival, and often taken into consideration when planning treatment for elderly cancer patients.[4,5] HRQOL may also associate with other cancer treatment selection determinants, such as quality of life preservation, patient treatment preference, socioeconomic background, physician-patient communication, etc.[6] It is therefore reasonable to inquire whether

and to what extent baseline HRQOL variables are associated with primary treatment selection in elderly men diagnosed with localized prostate cancer.

The association between life expectancy and primary treatment selection leads to strong confounding in observational studies that try to compare survival outcomes across different primary treatments. Adjustment for commonly considered confounders appears inadequate. Uncontrolled baseline HRQOL has been suspected to be a major source of residual confounding.[7,8]

Study Rationale

Health Related Quality of Life (HRQOL) and Cancer Treatment Selection

The concept of HRQOL was developed in accordance with the health definition of the World Health Organization (WHO). It embraces a wide range of clinically relevant dimensions, such as physical functioning, mental functioning, social functioning, and disease symptoms.[9] These health dimensions often influence cancer treatment decision. From a physician's perspective, they are hallmarks of overall health status, and therefore prognostic for life expectancy and tolerance for treatment related adverse events.[2-5] Physicians have been suggested to take HRQOL into consideration when planning treatment for localized prostate cancer. From a patient's perspective, HRQOL measures perceived health state in the context of culture and value system, which directly or indirectly reflect personal preference towards a particular treatment.[9-11] Exploration of the association between baseline HRQOL variables and primary treatment will help understand the complex treatment selection process in the elderly prostate cancer population.

The Confounding Effect of Baseline HRQOL

Confounding control is a central issue in epidemiological studies. A randomized, controlled trial (RCT) with a large sample size is the most ideal way to eliminate confounding.

However, it is difficult to conduct RCTs for localized prostate cancer with regard to survival outcomes because the mortality rate is low and a long follow-up time up to 10 years is required. Even though one such trial was completed and another trial is ongoing right now, they do not provide evidence to contemporary practice in a timely fashion. The Scandinavian Prostate Cancer Group Study No 4 study is the only completed high-quality randomized trial, which compared radical prostatectomy and expectant management in men with clinically detected prostate cancer between 1989 and 1999. The long term follow-up results were released in 2005.[12] This trial was conducted before the prostate specific antigen (PSA) screening became widely used. It is unknown whether the trial results apply to the current US prostate cancer population, most of who are diagnosed at an earlier stage of disease by the PSA blood test. The Prostate Cancer Intervention Versus Observation Trial (PIVOT) study is an on-going trial comparing radical prostatectomy and expectant management. This trial was initiated in 1994 and the patient recruitment completed in 2002. Ninety percent of the included patients were diagnosed with the PSA blood test. Unfortunately, the study results have not been released yet.[13]

Large clinical databases contain comprehensive longitudinal data collected from real-world practice settings. They are valuable research resources that are convenient, easy to access and concurrent. Thus, observational studies analyzing large clinical databases have and will continue to play a key role in comparative effectiveness research for localized prostate cancer. Previous observational studies showed a positive association between treatment aggressiveness and survival.[14-19] Nevertheless, unmeasured confounding, particularly unmeasured baseline HRQOL, was highly suspected to account for this observation instead of true treatment benefit. HRQOL incorporates multiple health domains that are not routinely available in most clinical databases, such as physical functioning, psychosociological functioning and disease symptoms. In the

context of prostate cancer, baseline HRQOL meets the classical definition of confounding. It associates with exposure (treatment selection), predicts outcome (survival), and cannot be affected by either exposure or outcome.[20] We are interested to examine the potential confounding effect of baseline HRQOL in a comparative observational study for localized prostate cancer treatment. The results of the proposed study will provide evidence and methodological recommendations to future research.

Purpose of the Study

We used the CaPSURE (Cancer of the Prostate Strategic Urologic Research Endeavor) database to investigate the association between baseline HRQOL variables and primary treatment selection in elderly men ($\geq$ 65 years old) diagnosed with localized prostate cancer. We hypothesized that some, if not all, baseline HRQOL variables are associated with primary treatment selection, independent of sociodemographic and clinical factors. Specifically, multinomial logistic regression was used to model the associations between the baseline HRQOL variables and primary treatment selection. The four types of primary treatments were included, which were radical prostatectomy, radiation therapy, expectant management and hormonal therapy. The included HRQOL variables were measured by three HRQOL instruments, which were the Karnofsky performance scale (KPS), the RAND 36-item health survey 1.0 (SF-36) and the UCLA prostate cancer index (PCI).[21] KPS is a single score reflecting physician-assessed functional status. SF-36 is an instrument for patient-reported general HRQOL. It measures eight health domains: physical functioning (PF), role-physical (RO), bodily pain (BP), general health (GH), vitality (VT), social functioning (SO), role-emotional (RE), and mental health (MH).[22,23] PCI is an instrument for patient-reported prostate cancer-specific HRQOL. It measures six health domains: sexual functioning (SF), bowel functioning (BF), urinary functioning (UF), sexual bother (SB), bowel bother (BB), and urinary bother (UB).[24]

Another purpose of the current study was to investigate whether and to what extent baseline HRQOL variables confound the association between primary treatment selection and survival outcomes in elderly men diagnosed with low- or intermediate-risk localized prostate cancer. Specifically, men treated with expectant management or hormonal therapy were pooled into a conservative treatment, and compared with men treated with radical prostatectomy or radiation therapy. The primary outcome was 10-year all-cause mortality. The magnitude of confounding bias was quantified by using the change-in-estimate criterion, which examines the relative changes in association estimates before and after adjustment for the baseline HRQOL variables in addition to commonly considered confounders.[20] A change of greater than 10% was considered contextually important. Different confounding adjustment methods were used. The propensity score method was used as it was done in the previous studies. The weighting methods were used to examine the confounding effect in accordance with the counterfactual outcome theory.[25-27] The counterfactual outcome theory based confounding requires a clearly defined target population of inference. Since men treated definitively are very different from men treated conservatively, three different weighting strategies were used. When weighting to the overall sample, the target population was represented by the entire study sample, regardless of the primary treatments they actually received. When weighting to the definitive treatment, the target population was represented by the men actually treated definitively. When weighting to the conservative treatment, the target population was represented by the men actually treated conservatively.

To further illustrate the confounding effect of baseline HRQOL, 10-year mortality due to prostate cancer and other reasons were compared. The rationale was that definitive treatment for localized prostate cancer would unlikely affect other cause mortality. At least, the effect size

would be smaller than that on prostate cancer-specific mortality. We expected to see that the difference in 10-year other-cause mortality, if there was any, diminished after additional HRQOL adjustment and the difference in 10-year prostate cancer-specific mortality remained.[7]

Research Questions and Hypotheses

Research Question 1

In CaPSURE elderly men (≥65 years old) diagnosed with localized prostate cancer, which baseline HRQOL variables are independently associated with primary treatment selection?

Research Hypothesis 1

The null hypothesis is that, none of the baseline HRQOL variables are independently associated with primary treatment, conditioning on cancer characteristics, sociodemographic and clinical variables. The alternative hypothesis is that, at least one baseline HRQOL variables are independently associated with primary treatment, conditioning on cancer characteristics, sociodemographic and clinical variables.

Research Question 2

In CaPSURE elderly men (≥65 years old) diagnosed with low- or intermediate- risk prostate cancer, do baseline HRQOL variables confound the association between primary treatment and all-cause survival, controlling for commonly considered confounders?

Research Hypothesis 2

The null hypothesis is that, the hazard ratio for all-cause mortality does not change significantly (=<10%) after adjustment for the baseline HRQOL variables in addition to commonly considered confounders. The alternative hypothesis is that, the hazard ratio for all-cause mortality changes significantly (>10%) after adjustment for the baseline HRQOL variables in addition to commonly considered confounders.

CHAPTER 2
LITERATURE REVIEW

This chapter is divided into three sections: 1) epidemiology of prostate cancer; 2) primary treatment selection for localized prostate cancer; 3) theoretical framework for confounding.

Epidemiology of Prostate Cancer

Prostate cancer is the most frequently diagnosed cancer in American men. About 1 in every 6 men in US will develop prostate cancer during their life time (life time risk of 15.6%). It has been estimated that 192,280 men in the United States were newly diagnosed with prostate cancer in 2009, which counted for approximately 25% of new non-skin cancer cases. Prostate cancer is also the second most fatal cancer in American men with an estimation of 27,360 deaths in 2009, which counted for approximately 9% all-type cancer death.[1]

Since PSA screening technology was introduced in early 1990s, most prostate cancers have been detected at early stage nowadays with low life-threatening risks. More than 90% of all prostate cancers are discovered at the clinically localized stage without regional involvement of pelvic lymph nodes or distant metastases. With increasing life expectancy and the introduction of more advanced screening techniques, the number of localized prostate cancer cases is expected to keep rising in the future.[1]

Advanced age is a strong prognostic factor for prostate cancer. According to the Surveillance, Epidemiology and End Results (SEER) database of the USA National Cancer institute, the median age at diagnosis was 68 years old. Approximately 63% of prostate cancer cases were diagnosed in men aged 65 years old or above. More than 70% of deaths due to prostate cancer occur in men aged 75 years old and above. The other two well established risk factors are race/ethnicity and family history. African American has the highest prostate cancer incidence rate in the world. The disease is more common in North America and northwestern

Europe than Asia and South America. Prostate cancer is also considered a hereditary disease. Recent genetic studies suggest that men who have a first-degree relative (father, brother, son) with prostate cancer have a two-fold to three-fold increased risk of developing prostate cancer, compared to men with no family history.[1,28]

Primary Treatment Selection for Localized Prostate Cancer

Primary Treatment Options

Standard primary treatment options for localized prostate cancer include radical prostatectomy, radiation therapy (including both external beam radiation therapy and brachytherapy), and expectant management, which is also referred as watchful waiting or active surveillance.[2,3] Hormonal therapy has been proposed as an alternative conservative treatment for men with clinically localized disease electing less aggressive management. Although not recommended by the current guidelines, its use has raised dramatically over the last decade in all risk categories.[29] Conclusive evidence regarding treatment efficacy in elderly patients is absent in the current literature. Only one high-quality randomized controlled trial was completed in Scandinavia countries, which compared radical prostatectomy vs. expectant management. The results favored radical prostatectomy over expectant management by showing a lower risk of cancer recurrence, cancer-related death and all-cause mortality after 10-year follow-up. However, the survival benefit appeared limited to a younger subgroup aged less than 65 years old.[12] Post-treatment quality of life is another important clinical outcome besides survival. Both radical prostatectomy and radiation therapy can result in detrimental effects on urinary, bowel and sexual function. Radical prostatectomy risks the same complications from major surgery as well as urinary incontinence and impotence. Radiation therapy imposes similar complications to patients with more significant bowel side effect and less severe urinary problems. Hormonal therapy also has side effects. It leads to hot flash, increased fatigue, difficulties with erection, and

declines in sexual interest and enjoyment.[30] Expectant management avoids active treatment related side effects. However, it increases patient perceived uncertainty, anxiety, and other mental burdens.[31,32]

Conceptual Model for Cancer Treatment Decision Making

Primary treatment selection for localized prostate cancer is a complex process. Based upon a general cancer treatment decision–making model developed by Zafar,[6] three parties are involved: physician, patient and patient's family (Figure 1). Factors contributing to physician treatment preference include knowledge of individual's disease, general disease knowledge and personal experience. Factors contributing to patient's treatment preference include socio-demographic characteristics, illness experience, quality of life concern, and disease status. Patient's family influences the treatment selection through modifying patient's preference. The final treatment decision is a result of active interactions between patients and physicians.

Factors influencing physician preference

Tumor characteristics. Tumor characteristics are the most important factor that physicians consider in primary treatment selection.[33] Three quantifiable systems have been well established to characterize prostate cancer. The TNM system refers to Tumor, Nodes and Metastasis. T staging indicates the size of the tumor. A higher T stage indicates the involvement of a larger proportion of the prostate. N staging indicates whether or not the cancer has spread into nearby lymph nodes. M staging indicates whether or not the cancer has metastasized. Clinically, localized prostate cancer is defined as T stage of T3a and below without evidence of lymph node involvement or metastatic spread. The Gleason grading system evaluates the microscopic pattern of the cancer cells. Higher Gleason scores indicate higher cancer aggressiveness. The prostate specific antigen (PSA) is a biomarker, the level of which is

positively associated with prostate cancer risks. Further, a risk stratification scheme for clinically localized prostate cancer has been developed synthesizing the three systems into one system:

- Low risk: PSA <10 ng/mL and a Gleason score of 6 or less and T stage of T1-T2a
- Intermediate risk: PSA between 10 to 20 ng/mL or a Gleason score of 7 or clinical stage T2b-T2c
- High risk: PSA ≥ 20 ng/mL or a Gleason score of 8 to 10 or clinical stage T2c or above

This risk stratification scheme has been widely adopted in current practice guidelines and serves as a basis for clinical decision-making.[2,3]

Life expectancy. Localized prostate cancer usually progresses very slowly. When the life expectancy is short, patients are very likely to die from competing risks before localized prostate cancer becomes a cause of morbidity and mortality. Therefore, life expectancy is a key consideration for physician to avoid treatments that might decrease quality of life without prolonging survival. A 10-year life expectancy rule has been generally accepted in the current clinical practice. According to the National Comprehensive Cancer Network (NCCN) guideline, radical prostatectomy is not recommended to patients with less than 10 years life expectancy.[34]

Life expectancy estimation can be very challenging, especially for elderly patients. In principle, chronological age is not a primary consideration in prostate cancer treatment decision. Elderly men who receive stage-appropriate therapy tend to do as well as their younger counterparts.[34,35] Life expectancy estimation should be based on an overall health status evaluation of co-morbidity, functional status, and other geriatric syndromes. Unfortunately, physicians have been criticized for being poor life expectancy estimators.[36]

The comprehensive geriatric assessment (CGA) has recently been developed to assist with the overall health status assessment for elderly patients. It assesses multiple geriatric dimensions, including comorbidity, functional status, physical performance, cognitive status, social support,

nutritional status, and polypharmacy.[2,34] Out of the comprehensive CGA health dimensions, comorbidity is the only well documented treatment predictor in the current literature. Patients treated with radical prostatectomy are found to have lesser number of comorbidities or lower co-morbidity index scores than those treated with non-surgical interventions, after adjusting for cancer and socioeconomic characteristics.[37-39] HRQOL overlaps CGA in multiple health dimensions. To our best knowledge, few studies have explored whether and to what extent HRQOL variables independently influence primary treatment selection for localized prostate cancer.

Physician characteristics. Survey studies show that prolonging survival is the most important outcome that physicians consider. One study indicated that 90% of physicians defined effectiveness as extending expected survival, in contrast to 43% of patients.[33] In the absence of solid evidence regarding survival superiority of one treatment over another, physician's expertise is one of the strongest predictors of treatment selection. A physician survey suggested that specialists prefer the treatment modality they deliver. That is, urologists almost universally identify radical prostatectomy as the best treatment option, while radiation oncologists almost universally identify radiation therapy as the best treatment option.[40]

A recent analysis of the SEER-Medicare database revealed consistent results. It was found that for those who consulted urologists alone only 5% underwent radiation therapy as primary treatment. For those who consulted both urologists and radiologists, over 80% underwent radiation therapy as primary treatment.[41] However, the observation was interpreted as a result of urologist's referral decision rather than the greater persuasiveness of radiologist. It was believed that urologists usually perform the biopsies that lead to a diagnosis of prostate cancer, and

therefore decide on the subsequent interventions. They would not refer a patient to radiation oncologists unless they feel radiation therapy as the optimal treatment.[42]

Factors influencing patient preference

Subjective opinion. Patient-centered treatment decision-making has been advocated for cancer management. Large amount of qualitative studies were conducted to explore the treatment decision-making process in men with early-stage prostate cancer. Zeliadt[6] reviewed 69 studies and concluded that substantial variations existed in what patients consider important in primary treatment selection. One example is that 18 different attributes of treatment were identified as being the "most important" in a small group of 60 patients.[43] In general, eradication of cancer is a key issue that concerns almost every patient upon diagnosis. However, patient treatment preference is often guided by personal belief and feeling rather than scientific evidence or logical reasoning. For example, radical prostatectomy is often preferred over radiation therapy by many patients because surgical removal of prostate is inaccurately believed to be the only way to cure cancer and radiation therapy is often inaccurately believed to be the backup plan. One study of elderly patients' willingness to accept radical prostatectomy versus expectant management showed that nearly half of the participants preferred radical prostatectomy even when radical prostatectomy was presented with zero survival benefit and 1 - 2% operative mortality risks.[44] Meanwhile, fear of surgery is one of the most popular reasons that patients choose radiation therapy and refuse radical prostatectomy.[45,46]

Treatment-related side effect is another important issue that concerns a significant proportion of patients.[6] In one large study involving 1,000 prostate cancer patients, approximately 45% defined treatment effectiveness as preservation of quality of life.[33] However, little is known how men tradeoff quality of life and quantity of life in their decision-making process. Current evidence shows that the treatment-related side effect has little impact on final

treatment decision, in spite of its significance stated by patients. One example is that more than 80% surveyed patients rated preservation of sexual function as a "very important" treatment goal, but only 3% of them indicated that "having few side effects" was the most important consideration in initiating therapy.[33]

Socioeconomic status. Analyses of large clinical databases revealed certain association patterns between socioeconomic characteristics and primary treatment of localized prostate cancer. Race/ethnicity has been identified to be a strong predictor for primary treatment selection. A common finding was that black men were less likely to receive radical prostatectomy than white men.[47-54] The possible explanations for this phenomenon include poor physician-patient communication and trust, more fear of surgery, more concerns about sexual functioning, more pessimism about the curability of prostate cancer, and lack of specifically designed decision aid tools for black men.[50,55]

Denberg[50,51] analyzed the SEER database and found a strong association between marital status and primary treatment, independent of cancer risks and other socioeconomic factors. Married men were more likely to receive aggressive treatments than unmarried men. One explanation for this observation is that married men or their wives advocate therapy that they perceive as likeliest to cure cancer, whereas unmarried men often lack social supports that would encourage aggressive interventions. Several qualitative studies also showed that patient wives tended to choose treatments that offered the best longevity and care less about treatment-related side effects.[56-58]

The impacts of income and education on primary treatment selection are less clear in current literature. Independent associations were found between primary treatments and income/education levels in several SEER studies that used ecological measures based on census

tract. Men living in lower income and education areas were more likely to use less aggressive treatments.[50,53,54,59] However, Yan[60] found no such associations when using individual level data from a prostate cancer screening program.

Illness experience. Patient treatment preference can be shaped by individual's prior health experience (co-morbidity, symptoms, psychological status, and so on). Current evidence is conflicting about how function and disease symptoms at diagnosis influences patient's treatment preference. Saigal[11] assessed patient utilities for treatment associated side effects among 401 men undergoing prostate needle biopsy. It was concluded that treatment preference did not differ by baseline urinary, sexual and bowel functions. Instead, the general health seemed to affect treatment preference. Men perceiving better general health tended to place higher value on survival and choose more aggressive treatments. On the opposite, men suffering from poor general health tended to place higher value on quality of life and choose less aggressive treatments. Zeliadt[10] surveyed 593 patients with newly diagnosed localized prostate cancer to assess whether preexisting genitourinary symptoms at the time of diagnosis influenced patients' preferences for radical prostatectomy vs. nonsurgical treatment. It was found that preexisting sexual dysfunction but not bowel or urinary dysfunctions was associated with considerations on treatment-related side effects. Men without sexual dysfunction at diagnosis appeared to care less about the risks of side effect than men with sexual dysfunction.

Physician-patient interaction

The physician-patient interaction is a critical stage in the conceptual cancer treatment decision-making model. It assumes an acceptable balance between the patient and physician in terms of shared decision making.[6] However, several qualitative studies showed that treatment selection process for localized prostate cancer is dominated by physicians. Patients often play a passive role, relying on physician's recommendations. In one group of patients that received

definitive treatments, urologists are rated as an important source of information by 95%-100% responders and the most important source of information by 70% of responders.[45] In a telephone survey of 421 randomly selected prostate cancer patients, 75% responders chose the first treatment that physicians ever recommended to them.[61] Davison[62] interviewed 25 men who decided to manage their low-risk prostate cancer with expectant management. The specialists' description of the prostate cancer was identified to be the most influential factor on patient's treatment decision-making. Quantitative studies of large clinical databases demonstrated strong associations between primary treatment received and specialist consulted, which indirectly confirmed the dominant role of physician in treatment selection.[41,63]

Lack of thorough physician-patient communication is another reason for the passive involvement of patients in the treatment selection process. Physicians often do not provide patients with the treatment-related side effect information, or provide the side effect information in a way that patients do not understand. One study showed that only 16% of surveyed patients recalled discussing side effects with their physicians, whereas nearly all surveyed physicians reported that they had thorough discussions about treatment related side effects with all their patients.[33] The inadequate communication about treatment-related side effects helps explain why treatment-related side effects concern patients but minimally influence final treatment selection. Patient sociodemographic characteristics seem to influence the patient-physician interaction. Qualitative studies showed that physicians selectively discussed the treatment options with patients. Black men and men from low socioeconomic class were often provided with less treatment options. These findings help explain the observed racial and socioeconomic disparities in primary treatment selection.[64]

Theoretical Framework for Confounding

Confounding Definitions

The concept of confounding is a central issue in epidemiology. Historically, the word confounding was used with different underlying meanings.[25] Three definitions of confounding are proposed in the current literature, which are the classical definition, collapsibility definition and counterfactual definition.[65]

Classical definition

The classical definition characterizes confounders by three criteria: 1) it must be a risk factor for the outcome among the unexposed; 2) it must be associated with the exposure in the source population from which the subjects arise; 3) it must not be affected by exposure or outcome.[20] Confounding occurs when confounders are not adjusted.

Although the classical definition is easy to understand and operate, it has several limitations. First, the observed association (or no association) between confounder and the outcome of interest or the exposure of interest may be spurious due to unknown variables. Confounder identification by using data based statistical techniques can be misleading and should be reserved when little prior information is available.[25] Secondly, a variable that satisfies the three criteria is not necessarily a confounder. Consider the directed acyclic diagram below (Figure 2): variable W satisfies all three criteria. It is associated with exposure X, predicts outcome Y, and not affected by either X or Y. However, W is not a confounder. On the contrary, controlling for W will introduce an non-causal association between X and Y.[20] This example implies that the three criteria are necessary but insufficient conditions for confounding.[20,25-27,66,67] Confounder identification must be grounded on an understanding of the causal pathways that links the variables under study. The causal pathways should always be evaluated against background disease risk, knowledge of subject matter, logical argument, evidence from previous

studies and other sources. Systematic tools have been developed to identify confounders such as the directed acyclic diagram.[20,26,68]

Collapsibility definition

The second confounding definition popularly used in the current literature is based on collapsibility. Collapsibility means that the effect measure of an exposure on an outcome is homogeneous across the strata of a covariate and the stratum specific measure equals to the marginal measure. In the situation of noncollapsibility where the stratum-specific effect measure and marginal effect measure are unequal, the covariate is a collapsibility definition based confounder.[20,25,65,67] Assume X is the exposure of interest, Y is the outcome of interest, and Z is a potential confounder. Let us further denote μ as the crude effect measure of X on Y, and denote μ^* as the stratum specific effect measure of X on Y, adjusting for Z. Z is a collapsibility based confounder when $\mu \neq \mu^*$. Change-in-estimate is the most popularly used criterion to quantify the confounding magnitude, which is a percentage difference between the crude effect measure and the stratum specific effect measure ($\frac{\mu^* - \mu}{\mu} X\ 100\%$).[20,69] A quantitative cutoff value is often specified in advance to determine whether a confounder is contextually important or not. For example, a confounder may be considered unimportant unless the change in effect measure is greater than 10%. The collapsibility definition of confounding also has limitations. First, non-collapsibility by itself does not necessary imply confounding. Change in effect measures after adjustment for additional variables may be caused by reasons other than confounding. It may reflect adjusting away the exposure effect when the adjusted covariate is an intermediate variable in the causal pathway between exposure and outcome; it may reflect the introduction of selection bias when the adjusted covariate is a common effect of both exposure and outcome;[68,70] it may also be an effect of measurement error rather than confounding.[71] Hence, same with the classical

definition, the collapsibility criterion has to be applied on top of a plausible causal linkage network. Secondly, the collapsibility definition depends on the chosen effect measures. Certain effect measures are not collapsible in nature, such as odds ratio, rate ratio and hazard ratio. The noncollapsibility nature reflects the inequality of marginal and stratum-specific effects, rather than confounding. These effect measures could change upon adjustment for a covariate that is not a confounder or remain same upon adjustment for a covariate that is a confounder. Vice versa, a variable can be identified to be a confounder according to one effect measure but not another one.[25,27,66,72] Thirdly, the noncollapsibility definition requires the homogeneity assumption, which assumes the effect measure to be constant across the strata of the potential confounder. It is unclear how to proceed when heterogeneity exists.

Counterfactual definition

The counterfactual definition of confounding is based on the counterfactual theory of causation, which views the effect of exposure as a contrast between the outcome in a target population when every unit is exposed and the outcome in the same population when every unit is unexposed. Because the same unit cannot be exposed and unexposed at the same time, one exposure condition must be hypothetical. The outcome under the hypothetical exposure condition is unobservable and called the counterfactual outcome. In practice, the counterfactual outcome is approximated from a substitute population that actually has the exposure condition. Confounding occurs if and only if the observed outcome from the substitute population differs from the counterfactual outcome. Confounders are any variables that cause the difference. Assuming the exposure is binary and the target population is exposed, let μ_1 represent the observed outcome of being exposed, μ_0 represent the counterfactual outcome had if the population been unexposed, and μ_0^* represent the observed outcome in an unexposed group.

Confounding occurs if and only if $\mu_0 \neq \mu_0^*$.[20,25,27,66] To quantify the confounding bias under the counterfactual definition, the following deductions can be made:

$$\mu_1/\mu_0^* = (\mu_1/\mu_0)(\mu_0/\mu_0^*) \Longrightarrow (\mu_1/\mu_0^*)/(\mu_1/\mu_0) = (\mu_0/\mu_0^*)$$

μ_1/μ_0 is the true effect measure, μ_1/μ_0^* is the biased estimate and μ_0/μ_0^* is the measure of the bias due to confounding, which is sometimes called the confounding risk ratio.[25]

Counterfactual theory based confounding definition automatically meet the classical definition. It has to causally affect the outcome and distribute unevenly between the substitute population and the target population. The confounder would not be an intermediate variable either because the substitute population and the counterfactual population are under the same exposure condition. The counterfactual definition of confounding has recently been advocated for several reasons: 1) it is specific regarding to causal inference and has a direct causal interpretation; 2) it does not make reference to a particular effect measure; 3) it offers solutions to time-dependent confounding that the classical and collapsibility definitions cannot solve appropriately. [25,27,65,67]

Confounding and selection bias

It should be noted that confounding and selection bias are sometimes used interchangeably in the currently literature when the bias is resulted from differential selection at start of follow-up. The present study adopts the criteria developed by Rothman, et al.[20]:

> …differential selection that occurs before exposure and disease leads to confounding, and can thus be controlled by adjustments for the factors responsible for the selection differences…In contrast, selection bias was usually described in epidemiology arises from selection affected by the exposure under study, and may be beyond any practical adjustment. (p. 138)

Therefore, the bias resulting from the uncontrolled baseline HRQOL is referred as confounding rather than selection bias in the current study.

The Rationale of Baseline HRQOL as Confounder

Previous observational studies reported a significant survival benefit of definitive treatment (radical prostatectomy or radiation therapy) relative to expectant management in elderly men diagnosed with low- or intermediate-risk localized prostate cancer.[15,16,18,19] These findings contradicted the finding from the Scandinavia randomized trial, which showed no survival benefit of radical prostatectomy vs. expectant management in patients aged 65 years old and above.[12] The implausible association was illustrated by Giordano[7] who replicated a SEER-Medicare study that found the definitive treatment associate with nearly 30% lower risks for prostate cancer-specific mortality and all-cause mortality relative to the expectant management. In addition to the similar findings on prostate cancer-specific mortality and all-cause mortality, the replicated study found definitive treatment strongly associated with significantly lower mortality risks resulting from other diseases. Moreover, patients that received radical prostatectomy were found to have even better survival than a cancer-free group. Given the assumption that prostate cancer interventions do not prolong survival from causes other than prostate cancer, these findings implied that the confounding bias was so strong that adjustment of SEER-Medicare variables was inadequate. It was further speculated that unadjusted baseline HRQOL might contribute to the uncontrolled confounding.[7]

As discussed in the previous section, confounding identification requires prior knowledge of causal pathways. When the primary outcome is mortality, any independent mortality predictors at baseline besides primary treatment should be carefully considered as confounder candidates. The Medicare administrative database is primary developed for reimbursement purposes. It contains little health status information other than diagnostic codes. Many relevant health dimensions are omitted, such as functional status, social support, frailty etc. In addition, the generic co-morbidity measures based diagnosis codes from administrative databases have

been criticized for poorly reflecting the health status of the elderly population. First, under-diagnosis is common in elderly patients. New symptoms may not be recognized or dismissed as manifestations of pre-existing conditions.[73] Secondly, current diagnosis coding systems have limited capability of reflecting disease severity. Comorbidity measures based on diagnosis code, such as number of comorbidities and comorbidity indices, assume that each constituent comorbid condition has the same impact, and that comorbid conditions with the same diagnosis code are equally severe. Unfortunately, this is often not true. Clinical prognosis often varies greatly in patients carrying the same diagnosis codes.[74-77]

The potential confounding role of baseline HRQOL can be attributed to its nature as health status measures. In the present study, the general HRQOL is measured by SF-36. This instrument has been validated in a large sample of 9,897 elderly patients, aged from 65 to 104 years old.[4,22,23,34,76,78-80] It includes nine domains that address different aspects of health. For example, the physical functioning scale measures limitations in behavioral performance of everyday physical activities; role functioning scale measures the extent of disability in everyday activity due to physical problems; the social functioning scale and role-emotional scale measure limitations or disability due to personal or emotional problems. The HRQOL also measures disease symptoms. SF-36 has specific scales addressing body pain and fatigue, two common symptoms for many diseases. The PCI concerns prostate cancer related symptoms regarding urination, sexuality and bowel function.

HRQOL often correlates with disease severity. For instance, Faller[81] found that the SF-36 composite scores independently predicted survival in patients with chronic heart failure. The prognostic values were mainly due to the strong correlations with the heart failure severity and depression severity. Furthermore, HRQOL correlates with patients' income level, social support,

outlook, and attitudes. These factors often affect the patients' ability to manage their cancer and comorbidities, but would not be captured in regular clinical examinations.

Overall, baseline HRQOL variables measure multiple dimensions of health status. Adjustment of HRQOL variables in conjunction with commonly used demographic and co-morbidity variables may help reduce the residual confounding. This effort will be particularly fruitful for older men who often simultaneously have multiple comorbid conditions, impaired functional status, decreased social support and other characteristics for poor outcomes.

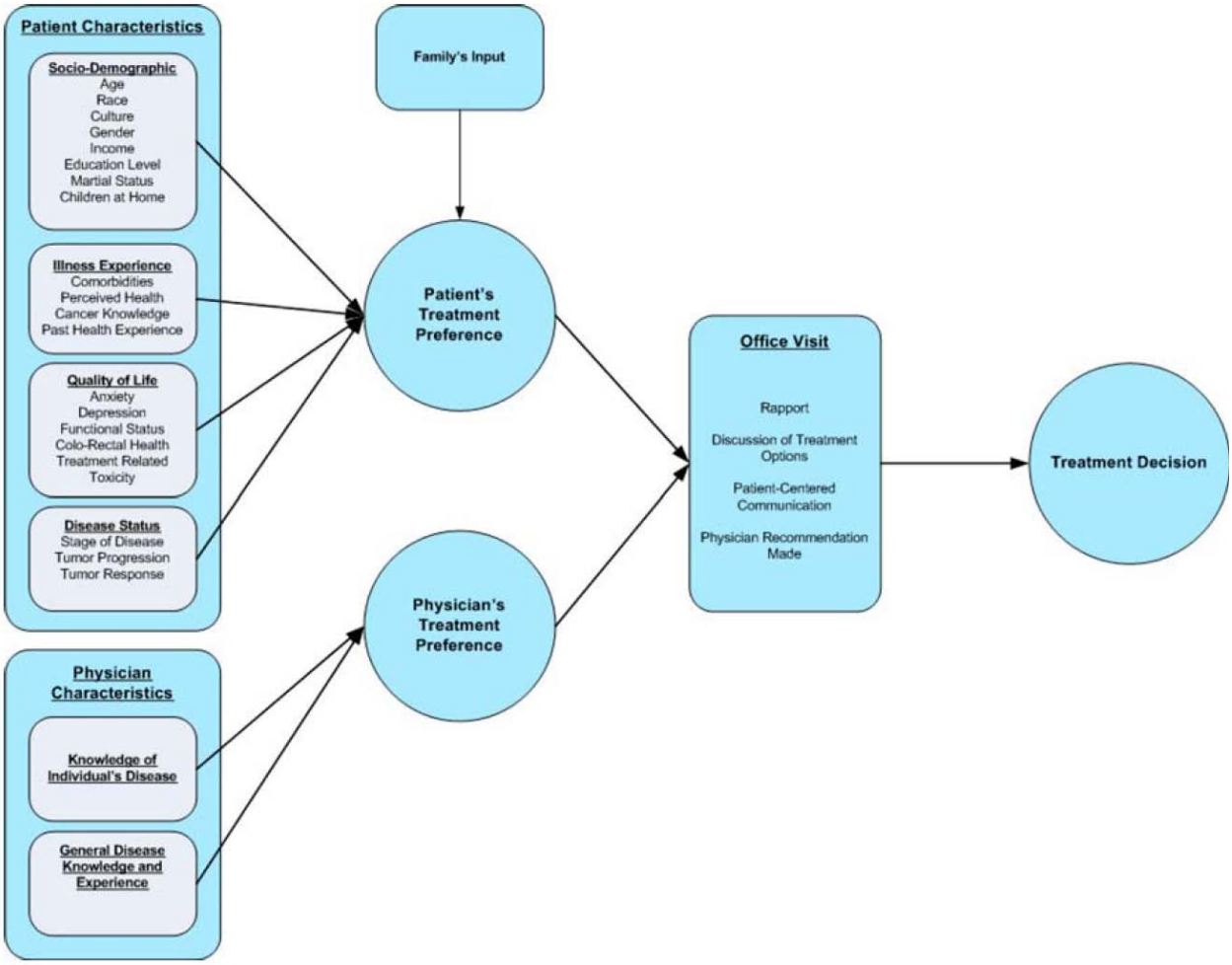

Figure 2-1.Conceptual model for patient and physician cancer treatment selection. Source: Zafar et al. 2006.

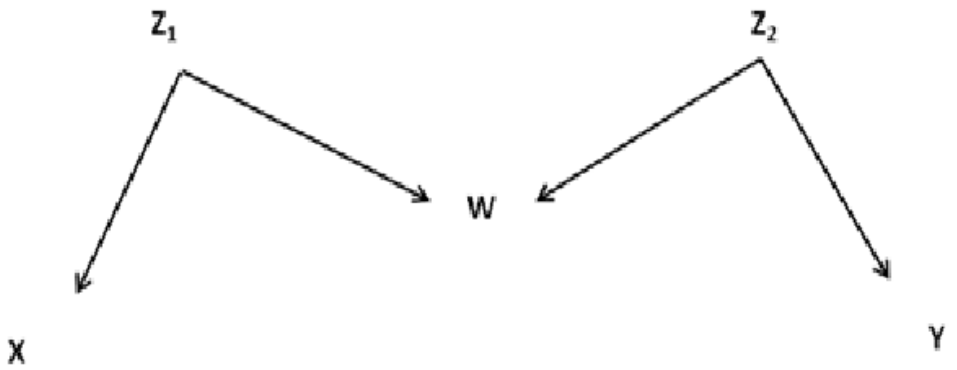

Figure 2-2.A directed acyclic gram under which the classic confounder criteria fail. Source: Rothman et al. Modern Epidemiology Third Edition.

CHAPTER 3
METHODOLOGY

The methodology chapter consists of four parts: 1. description of the data source – the CaPSURE database; 2. study design and sample selection; 3. descriptive analysis; 4. multivariate statistical analysis.

Data Source

The Cancer of Prostate Strategic Urologic Endeavor (CaPSURE) was the primary data source for the proposed study. CaPSURE is a large prostate cancer registry maintained by the Urology Department University of California, San Francisco since 1995. The primary goal of CaPSURE is to evaluate the impact of prostate cancer treatments on clinical, economic, and quality of life outcomes. It longitudinally follows biopsy-proven prostate cancer patients in a naturalistic setting. Patients are enrolled from thirty-seven community urology practices, three academic medical centers and three veteran affair hospitals throughout the United States.

All patients with biopsy-proven prostate cancer are invited to join the study by their urologists at the time of a clinical visit, irrespective of disease duration, severity or treatment type. Newly enrolled patients are followed prospectively until death or withdrawal from the study. Upon a form of consent is signed, data are collected from both urologists and patients. Urologists provide comprehensive clinical assessments of their patients at the time of first enrollment, gathering the data relevant to prostate cancers, including laboratory test results, pathological staging, initial and following treatments used, and important dates. During the follow-up time, urologists further collect treatment and clinical data at each clinic or office visit. Patients complete questionnaires regarding their demographics, comorbidity, quality of life, satisfaction of care and healthcare resource utilization when they first join CaPSURE. During the follow-up time, patients are mailed questionnaires every 6 months to update their quality of life,

satisfaction with care, severity of co-morbid conditions, and health care resource utilization. After patient mortality is reported by participating clinicians or the next of kin, a copy of the state death certificate is obtained and a determination of the cause of death (prostate cancer-specific vs. other-cause) is made by consensus of the study investigators. In general, death is considered to be prostate cancer-specific if prostate cancer is listed as a primary, secondary, or tertiary cause of death and no other malignancy was listed as a higher order cause. For patients whose state death certificate is unavailable, the National Death Index will be queried to identify date and cause of death. More details about CaPSURE have been published elsewhere.[21]

Study Design and Sample Selection

A cross-sectional study design was used to investigate the associations between baseline HRQOL variables and primary treatment selection in elderly men diagnosed with localized prostate cancer. The type and date of primary treatment received were recorded in CaPSURE. One advantage of CaPSURE was that the primary treatment was confirmed by doctors, which avoided potential treatment misclassification. A 9-month time window (278 days) after diagnosis was used for primary treatment identification. Patients were classified into the radical prostatectomy group if they received the procedure during the time window, regardless of neo-adjuvant therapy or adjuvant therapy. Patients were classified into the radiation therapy group when they received brachytherapy or external beam radiation as primary treatment during the time window, regardless of neo-adjuvant therapy and adjuvant therapy. Patients were classified into the hormonal therapy group if they received bilateral orchiectomy, luteinizing hormone-releasing hormone, agonist, antiandrogen, diethylstilbesterol, or finasteride therapy alone or in any combination during the time window without any additional definitive treatment. The remaining patients were classified into the expectant management group as they did not receive

any of the three interventions above and doctors checked the "expectant management" box in the questionnaire. The following sample selection criteria were further applied:

- Newly diagnosed with prostate cancer in year of 1995 or later. In CaPSURE, the diagnostic biopsy date is used as the diagnosis date, which is available for approximately 90% of enrolled patients.[29] The requirement of diagnosis year of 1995 or later was to ensure prospective follow-up since CaPSURE enrollment started in 1995.
- Newly diagnosed with prostate cancer at age of 65 years and older.
- No evidence of lymph node involvement (N1) or metastasis (M1) at diagnosis.
- Patients were excluded if no prostate cancer intervention was indicated and they were lost to follow-up within 9 months after diagnosis.
- Baseline HRQOL data availability. For radical prostatectomy, radiation therapy, and hormonal therapy groups, "baseline" was defined as the periodfrom90 days before the diagnosis date to the treatment date. For the expectant management group, "baseline" was defined as the period from 90 days before diagnosis date to 278 days after diagnosis.

A retrospective cohort study design was used to investigate the potential confounding role of baseline HRQOL variables when comparing primary treatments with regard to survival outcomes in elderly men aged 65 years old or above. Because expectant management is not recommended for high-risk prostate cancer, this section further concentrated on elderly men with low- or intermediate-risk prostate cancer. The cancer risk level was determined by Gleason score and T stage as described in the previous studies.[18] Patients were excluded if they had Gleason score sum more than 7 or T3/T4 stage.

The radical prostatectomy and radiation therapy groups were collapsed into a definitive treatment group. The expectant management and hormonal therapy groups were collapsed into a conservative treatment group. These two groups were compared with regard to all-cause mortality, prostate cancer-specific mortality, and other-cause mortality in 10-year follow-up. Because we found men treated with radical prostatectomy were quite different from men treated

with radiation therapy in a wide range of baseline characteristics, both treatments were also compared with conservative treatment separately.

Descriptive Analysis

Descriptive analyses were performed for the following variables:

- The primary treatment received
- Baseline sociodemographic variables
- Baseline prostate cancer variables
- Baseline BMI and comorbid variables
- Baseline Karnofsky performance score
- Baseline SF-36 scores
- Baseline PCI scores

All these HRQOL variable were numeric, ranging from 0 – 100. Their distributions were summarized by mean ± SD and median with inter-quartile. Because these HRQOL scores were highly skewed, they were dichotomized for analyses. The SF-36 scores were dichotomized at population median for male aged 65 years old or above.[22] The PCI scores and KPS were dichotomized at the sample median, as the population norms are not available. For those variables where the median was 100, patients were divided into two groups of 100 vs. <100. The crude associations between treatment and baseline variables were examined by using univariate logistic regression. The crude associations between the baseline variables and survival outcomes were examined by using univariate Cox regression analysis.

Multivariate Statistical Analysis

Missing Data Imputation

The CaPSURE collected data by using questionnaires completed by both patients and physicians. A small portion of baseline data was missing. To preserve statistical power, missing data were imputed by using the multiple imputation (MI) technique.[82] MI assumes “missing at random”, which means that missing data depend on known values, and accounting for the known

values produces unbiased results. Compared to the single imputation methods, MI not only reflects the natural variability in the missing data, but also incorporates the uncertainty of unknown missing value prediction. Further, multiple imputation has been shown robust to departures from normality assumptions and provides adequate results in the presence of low sample size or high rates of missing data.

The method for imputation and subsequent analysis of the filled-in data involved three steps: 1) imputing data to obtain 5 copies of the filled-in data set; 2) carrying out standard statistical analyses on each dataset separately to obtain desired parameter estimates and standard errors; and 3) combining results of the five analyses by computing the overall estimations and a variance estimate that includes both a within imputation and an across-imputation component. For the first step, the SAS procedure of PROC MI and the Markov chain Monte Carlo (MCTC) method were used to generate the five imputed datasets. As a general rule for building the imputation model, using all available information maximizes certainty and minimizes bias. All of the baseline variables together with the follow-up time log transformation were included into the imputation model. SAS requires the imputed values to be numeric. Dummy variables were setup for all categorical variables before imputation. The imputed values remained unrounded in analysis to avoid potential bias since the primary goal of imputation was to account for the missing data uncertainties rather than getting plausible values. Besides, none of the categorical variables was the primary interest of the present study.[83] The planned statistical analyses were conducted in each of the five imputed datasets. The SAS procedure of PROC MIANALYZE was used to combines the results. More details regarding how to analyze the imputed datasets are described in the following sections.

Multinomial Logistic Regression

A multinomial logistic regression model was used to examine the associations between the baseline variables and primary treatments. The dependent variable was primary treatment with four categories: radical prostatectomy, radiation therapy, expectant management, and hormonal therapy. The independent variables were the baseline sociodemographic, clinical, and HRQOL variables. The formulation of the multinomial logistic regression is given by the following equation:

$$\text{Log}\left[\frac{\pi_j}{\pi_J}\right] = \alpha + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_i X_i$$

- J denotes the number of outcome categories.
- π_J denotes the probability of the baseline outcome category.
- π_j denotes the probability of the comparison outcome category.
- $X_1 - X_i$ denote independent variables that associated with the treatment selection.
- $\beta_1 - \beta_i$ denote the association parameters for the independent variables.

Bivariate analyses were performed to examine the crude associations between primary treatment selection and individual baseline variables. Multivariate analyses were performed to examine the independent associations between baseline HRQOL variables and primary treatments, adjusting for the baseline sociodemographic and clinical variables. The multivariate analysis was completed in three steps. Step 1: A preliminary multinomial logistic regression analysis was constructed to select all baseline sociodemographic and clinical variables that was significantly associated with primary treatments. An automated backward variable selection procedure was used with stay criteria of P=0.05 while forcing in age and cancer risk level. Step 2: The HRQOL variables entered the preliminary model individually to determine their independent associations with the primary treatments by using log likelihood test. All the preselected sociodemographic and clinical variables were forced in. Step 3: All HRQOL variables entered the preliminary model at the same time and the most predictive HRQOL

variables were determined by using the backward elimination procedure with a stay criterion of P=0.05. All the preselected sociodemographic and clinical variables were forced in. Because the multiple imputation procedure produced five imputed datasets, all the variable selection processes were first performed in each dataset. The final selected variables had to retain in at least three datasets.

Cox Proportional Hazard Model

Cox proportional hazard model was used to compare the survival outcomes between the definitive treatment and the conservative treatment. Both propensity score and weighting methods were used to adjust for baseline confounders. All analyses were performed twice, without and with baseline HRQOL variables considered in addition to sociodemographic and clinical variables. The two hazard ratios were compared to assess the confounding magnitude of the baseline HRQOL variables by using the change-in-estimate criterion. Both relative and absolute changes were calculated.

Because of the immortal time concern, the starting time point was the treatment date for radical prostatectomy, radiation therapy, and hormonal therapy. The starting time point for expectant management was the 278th day after the diagnosis date. Patients who did not have an event of interest were censored when they died from unrelated reasons, dropped out CaPSURE, or the end of the study period. The proportional hazards assumption was checked by plotting log-log functions. The formulation of the Cox proportional hazard model is given below:

$$\lambda(t) = \lambda_0\ (t)\exp\ (\beta_{tx}X_{tx} + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_i X_i)$$

- $\lambda(t)$ denotes individual i's hazard to experience an event of interest at time t.
- $\lambda_0(t)$ denotes baseline hazard function at time t.
- X_{tx} denotes the dummy variables of individual's treatment category (conservative treatment was the reference category).

- β_{tx} denotes the association parameters of definitive treatment.
- $X_1 - X_i$ denote the covariates, which was the propensity score in current study.
- $\beta_1 - \beta_i$ denote the association parameters for the covariates.

Informative Censoring Adjustment

Another key assumption for Cox proportional hazard model is random censoring, which means that an individual's censoring time is independent of his failure time. Non-random censoring would lead to selection bias.[70] The inverse-probability-of-censoring-weighting (IPCW) method introduced by Robins was used to correct the selection bias due to informative censoring.[13] The IPCW weights were proportional to the inverse of the probability of surviving uncensored, conditioning all the outcome predictors. In the current study, the 10-year follow-up time was divided into 120 intervals with 30 days in each. The probability of being uncensored was calculated for each interval by using logistic regression. The dependent variable was censoring status (non-censored vs. censored), and the independent variables were all baseline sociodemographic, clinical and HRQOL variables. Three IPCW weights were calculated for all-cause, prostate cancer-specific, and other-cause mortality, respectively. Because the localized prostate cancer interventions were point treatments, there was little concern on time dependent confounding. The 95% confidence intervals were obtained based on 1,000 bootstrap samples for all the Cox regression analyses.

The formulation to estimate stabilized IPCW weights can be simplified as below for point interventions without time dependent confounding:

$$sw_i = \prod_{k=0}^{t} \frac{\Pr[C(k) = 0 | \bar{C}(k-1) = 0,\ Z = Z_i]}{\Pr[C(k) = 0 | \bar{C}(k-1) = 0, Z = Z_i, X = X_i]}$$

- C denotes the censoring status, where 0 refers to non-censored and 1 refers to censored.
- k denotes the time intervals, which was 1-120 in the current study
- Z denotes the primary treatment received (definitive treatment or conservative treatment).

- X_i denotes the risk factors for outcome.

Propensity Score Method

Propensity score method was used in the previous studies comparing localized prostate cancer treatments. It was introduced by Rosenbaum and Rubin, defined as the conditional probability of receiving a particular treatment given a set of observed covariates.[84] Assuming that the treatment and outcome are conditionally independent given the covariates, the difference between the two compared groups is an unbiased estimate of the average treatment effect, controlling for the single propensity score. A major advantage of propensity score is to synthesize a large collection of covariates to a single summary measure. This is very useful when outcomes are rare and treatment is common, which was exactly the situation in the current study. The propensity score was estimated by using multivariate logistic regression. The dependent variable was the treatment received. The independent variables were potential confounding variables. It has been recommended to include all risk factors for the outcome into the propensity score model, regardless of their associations with treatment.[85] While previous studies included comorbidity indices (e.g. 0 vs. 1 vs. 2 vs. 3 or more) in their propensity score models, we found diabetes and neurological disease/stroke could not be balanced in that way. Both comorbidities remained associated with treatment ($P<0.05$). Therefore, all the 11 individual diseases and the presence of other disease (0 vs. at least 1) were included in the propensity score model. Below is the equation for propensity score calculation.

$$P_i = \frac{e^{\alpha+\beta_1 X_1+\beta_2 X_2+\cdots+\beta_i X_i}}{1+e^{\alpha+\beta_1 X_1+\beta_2 X_2+\cdots+\beta_i X_i}}$$

- P_i denotes individual i's propensity score, which was the probability of receiving definitive treatment as primary treatment given baseline characteristics.
- $X_1 - X_i$ denote covariates, which were the sociodemographic, clinical and HRQOL variables at baseline.

- $\beta_1 - \beta_i$ denote the association parameters for $X_1 - X_i$.

Two propensity score models were developed separately. The reference model included all sociodemographic and clinical variables that were commonly used in the previous studies. The HRQOL model included the dichotomized baseline HRQOL variables additionally. Propensity scores generated from either model were compared in terms of distributions and confounder balancing performance.

There are three commonly used techniques to adjust confounding by propensity scores: matching, stratification, and regression. To be consistent with the previous studies, we chose the regression adjustment and included the propensity score as a continuous covariate in the Cox proportional hazard model. Because the propensity scores were skewed, the analyses were repeated adjusting for propensity score quintiles as a categorical variable, which avoided the linearity assumption.[86] The hazard ratios for all-cause mortality were also examined within each propensity score quintile, looking for effect heterogeneity.

We did not use propensity score matching for two main reasons: 1) the propensity scores did not overlap substantially. Matching might lose significant amounts of patients that did not have matches. It would be difficult to characterize the finally matched patients, and therefore would not know to which population the study conclusion might generalize to. 2) We intended to compare the reference propensity score vs. HRQOL propensity core. Matching by two different propensity scores might result in two different matched samples. It would be difficult to tell whether any differences were due to the additional HRQOL adjustment or due to the different characteristics of the two matched samples.

Weighting Methods

The hazard ratio obtained from propensity score regression adjustment is a maximum-likelihood estimate, which aims to maximize the probability of the data under a homogeneity

assumption. It does not necessarily produce a causal estimate based on the counterfactual theory of causation, particularly when effect modification presents.[20,84,87] The confounding role of baseline HRQOL variables was investigated according to the counterfactual theory by using two weighting methods, inverse-probability-of-treatment-weighting (IPTW) and standardized-mortality-ratio-weighting (SMRW).[30,31,88,89] Both weighting methods create pseudopopulations in which covariates included in weight calculations are no longer associated with the treatment. When exposure is a point treatment, which is the case in the present study, both weighting methods can be interpreted as multivariable standardization methods that use different standard populations. Given no unmeasured confounders and correct weighting model specification, the IPTW method estimates the average treatment effect in a population, the risk factor distributions of which are equal to those in the entire sample. The SMRW method estimates the average treatment effect in a population, the risk factor distributions of which are equal to those in one comparison group. The propensity score, IPTW and SMRW estimates would be similar unless the comparison groups have very different risk factor distributions that modify the treatment effect.[32,84,87]

The weights can be easily calculated from the propensity score. The equations are given below. When weighting to the entire sample, the weights were proportional to the inverse probability of receiving the treatment that was actually received. One concern was that a few patients can have extremely large weights and dominate the weighted analysis. A stabilized weight was used instead to mitigate this situation, which timed the weights by the overall probability of receiving the treatment in the entire sample. When using the SMRW method, we estimated the average effect in both the definitive treatment and conservative treatment groups separately. When weighting to the definitive treatment group, the weights were 1 for men in the

definitive treatment group and the propensity odds for men in the conservative treatment group. When weighting to the conservative treatment group, the weights were the inversed propensity odds for the definitive treatment group and 1 for the conservative treatment group. The weight calculation formulations are given below:

Weighting to the entire sample: $w_{DT} = \frac{P}{P_i}$; $w_{CT} = \frac{1-P}{1-P_i}$

Weighting to the definitive treatment group: $w_{DT} = 1$; $w_{CT} = \frac{P_i}{1-P_i}$

Weighting to the conservative treatment group: $w_{DT} = \frac{1-P_i}{P_i}$; $w_{CT} = 1$

- W_{DT} denotes the weight for men in the definitive treatment group
- W_{CT} denotes the weight for men in the conservative treatment group
- P denotes the unconditional probability of receiving definitive treatment in the entire sample
- P_i denotes the propensity to receive the definitive treatment

Two set weights were generated separately. One set was calculated by the reference propensity score, considering all the baseline sociodemographic and clinical variables. The other set was calculated by the HRQOL propensity score, considering the baseline HRQOL variables additionally. Two hazard ratios obtained by using either weight were compared to assess the potential confounding magnitude of baseline HRQOL variables per target population. Weighted survival curves were plotted following the method developed by Westreich[90] for all the three weighting methods.

CHAPTER 4
RESULTS

Association between HRQOL and Primary Treatment

Descriptive Analysis

The baseline HRQOL data were available for 3,775 CaPSURE men. Their enrollment times were between March 21st, 1995 and October 11th, 2007. After the selection criteria were applied, a cohort of 1, 924 men were selected. They were all newly diagnosed with localized prostate cancer at age of 65 years and older, without lymph nodes involvement or metastasis. Based on the 9-month primary treatment determination window, 676 men received radical prostatectomy (34.8%), 815 men received radiation therapy (35.7%), and 172 men received hormonal therapy (8.4%). The remaining 261 men were classified into the expectant management group (21.1%). The average follow-up time from prostate cancer diagnosis to death or censoring (end of follow-up or loss to follow up) was 4.4 years (SD=2.5). The follow-up time appeared to be similar across the four treatment groups. The length of time between prostate cancer diagnosis and baseline data collection was also examined. In the entire cohort, the mean length of time was 44 days (SD=38) and the median was 33 days (IQR: 18-56). The length of time was similar across the four treatment groups.

Baseline sociodemographic characteristics are presented in Table 4-1. There were small amounts of missing data in each variable except for age and diagnosis year. The proportion of missingness ranged from 2.0% in race to 12.7% in annual household income. The missing data pattern was similar across all four treatment groups, with slightly higher rates in the expectant management group. The mean age of the entire cohort was 72 years (SD=5) and the median age was 71 years old (IQR=68-75). Regardless of missingness, the included men were predominantly white, married, covered by Medicare, and non-smokers. Their education and household income

looked relatively high. More than 80% men were above high school graduates, and 36.0% men were college graduates or above. Only 14% men reported their annual household income below $20,000. The $20,000-$50,000 category accounted for 42.4%, and the > $50,000 category accounted for 30.6%. About 12.7% annual household income data were missing. Approximately two third of the entire sample were diagnosed after 2001.

Baseline clinical characteristics are presented in Table 4-2. Approximately 2-5% clinical data were missing. The missing data pattern was similar across the four treatment groups, with slightly higher rates in the expectant management group. According to the NCCN guideline classification, low and intermediate-risk prostate cancer accounted for 40.4% and 41.3% in the entire cohort, respectively. Only 13.3% men had high-risk prostate cancer at diagnosis, while 4.9% men had incomplete cancer information. Obesity (BMI≥30) and overweight (BMI: 25-29.9) accounted for 19.2% and 48.0%. Normal weight (BMI<25) accounted for 29.0%, while 3.6% BMI data were missing. Approximately 91% men reported one or more comorbidities. Men having 1, 2, and 3 or more comorbidities accounted for 24.0%, 27.8%, and 36.8%, respectively. Missing data accounted for 2.7%. Regarding specific disease type, the most prevalent ones were hypertension (49.7%), arthritis (45.0%), and heart disease (27.7%). Moreover, 90.1% men reported at least one other type diseases that were not on the comorbidity checklist.

Baseline HRQOL data are presented in Table 4-3, which included the Karnofsky performance score (KPS), eight Medical Outcome Short Form 36 (SF-36) scores, and six UCLA-prostate cancer index scores (PCI). All these HRQOL variables were numerical, ranging from 0-100. Substantial missingness was observed for KPS, which accounted for 65.2% in the entire cohort. The missingness in SF-36 and PCI was less than 6.0%. The missing data pattern was

similar across all four treatment groups, with slightly higher rate in the expectant management group. Regardless of the missingness, the included men appeared to have fairly good HRQOL at diagnosis for their age group. The median KPS was 100. The median SF-36 scores were all above or equal to the population median. The median PCI urinary and bowl scores were 100 or near 100. The two sexual related scores were low, with median values around 50. All HRQOL variables were dichotomized into high score vs. low score. The KPS and PCI scores were dichotomized at the sample median. The SF-36 scores were dichotomized at the US population median.[22]

Crude Associations between Baseline Variables and Primary Treatment

The crude associations between the baseline characteristics and primary treatment were examined by using bivariate multinomial logistic regressions. Missing data were imputed by using the multiple imputation technique as described in the method section. Table 4-4 shows the crude odds ratios and 95% confidence intervals for baseline sociodemographic variables. Radical prostatectomy was strongly associated with younger age, married, higher education level, higher household income level, and being diagnosed in 2001 or after. Besides, the radical prostatectomy group was more likely to be white than the hormonal therapy group, and more likely to have Medicare coverage than radiation therapy. The differences among the other three groups were much less pronounced. Compared with expectant management and hormonal therapy, radiation therapy was associated with younger age and being married. The radiation therapy group was also more likely to have higher education level than the expectant management group. The two conservative treatment groups did not significantly differ from each other.

Table 4-5 showed the crude odds ratios and 95% confidence intervals for the baseline clinical variables. Radical prostatectomy and radiation therapy were associated with higher prostate cancer risk level than expectant management, while hormonal therapy was strongly

associated with higher prostate cancer risk than all the other three treatments. High BMI appeared to associate with the two definitive treatments than the two conservative treatments. The radical prostatectomy group had the least number of comorbidities than the other three treatment groups. Regarding individual comorbidity, the radical prostatectomy group was less likely to have heart disease, neurological disease/stroke, other cancer, diabetes, hypertension, and lung disease. The differences among the other three treatment groups were less pronounced.

Table 4-6 shows the crude odds ratios and 95% confidence intervals for the dichotomized baseline HRQOL variables. Radical prostatectomy was associated with high KPS than radiation and hormonal therapy. Radical prostatectomy was also significantly or borderline significantly associated with high scores for nearly all the SF-36 and PCI variables. Radiation therapy was associated with high HRQOL scores than the conservative treatments for most baseline HRQOL variables, although not as significant as radical prostatectomy. Compared with expectant management, radiation therapy group was more likely to have high scores for three SF-36 variables: physical functioning, role physical and general health. Compared with hormonal therapy, the radiation therapy group was more likely to have high scores for all SF-36 variables except for role emotional and mental health, Radiation therapy group was also more likely to have high scores for three PCI variables: bowel functioning, bowel bother, and sexual functioning. There was little difference between expectant management and hormonal therapy except that the expectant group was more likely to have high KPS and sexual functioning scores.

Adjusted Associations between Baseline HRQOL and Primary Treatment

Multivariate analyses were conducted to investigate the independent associations between the baseline HRQOL variables and primary treatment, adjusting for sociodemographic and clinical factors. First, a preliminary multinomial logistic model was fit with all baseline sociodemographic and clinical variables by using a backward elimination procedure, while

forcing in age and prostate cancer risk level. Sociodemographic variables retained in the preliminary model were age, race, marital status, income level, insurance type, and diagnosis year. Clinical variables retained in the preliminary model were cancer risk level, heart disease, neurological disease/stroke, diabetes, lung disease, kidney disease, and urinary condition.

Next, log likelihood tests were used to investigate whether any dichotomized baseline HRQOL variables were significantly associated with primary treatment when added into the preliminary model. Six HRQOL variables were identified, including KPS, four SF-36 variables and one PCI variable. The four SF-36 variables were physical functioning, role-physical, general health, and vitality. The one PCI variable was sexual functioning. Table 4-7 presents the adjusted odds ratios and 95% confidence intervals. For men with high KPS, the estimated odds of receiving radical prostatectomy was 1.60 (95% CI: 1.00-2.57) times the estimated odds of receiving radiation therapy, and 1.86 (95% CI: 1.16-2.99) times the estimated odds of receiving hormonal therapy. High KPS was associated with a higher likelihood of receiving expectant management as primary treatment than hormonal therapy (OR: 1.81, 95% CI: 1.00-3.27).

Regarding the four SF-36 variables, high scores were significantly associated with higher likelihood of receiving radical prostatectomy as primary treatment than the other three treatments. For men with high physical functioning score, the estimated odds of receiving radical prostatectomy as primary treatment was 1.96 (95% CI: 1.41-2.71), 2.22 (1.44, 3.42), and 2.78 (95% CI: 1.75-4.41) times the odds of receiving radiation therapy, expectant management, and hormonal therapy as primary treatment, respectively. For men with high role-physical score, the three odds ratios were 1.36 (95% CI: 1.02-1.81), 1.94 (95% CI: 1.30-2.88), and 1.66 (95% CI: 1.07-2.58). For a high general health score, the three odds ratios were 1.55 (95% CI: 1.15-2.09), 2.04 (95% CI: 1.36-3.04), and 2.35 (95% CI: 1.50-3.69). For a high vitality score, the three odds

ratios were 1.74 (95% CI: 1.32-2.28), 2.14 (95% CI: 1.45-3.17), and 2.62 (95% CI: 1.71-4.02). Men with high role physical were also 1.43 (95% CI: 1.02-1.99) times more likely to receive radiation than expectant management. Men with high general health and vitality scores were also 1.52 times (95% CI: 1.03-2.23) and 1.51 times (95% CI: 1.04-219) more likely to receive radiation therapy than hormonal therapy, respectively. Expectant management and hormonal therapy did not differ in any SF-36 variables after covariate adjustment.

Sexual function was the only PCI variable found to independently associate with treatment selection, adjusting for sociodemographic and clinical factors. Men with high sexual function score were 1.35 (95% CI: 1.06-1.72) times more likely to receive radical prostatectomy than radiation therapy, 1.77 (95% CI: 1.17-2.70) times more likely to receive radical prostatectomy than hormonal therapy, and 1.71 (95% CI: 1.09-2.67) time more likely to receive expectant management than hormonal therapy.

Lastly, the most predictive HRQOL variables were determined by fitting all HRQOL variables into the preliminary model simultaneously. A backward elimination procedure was used, while forcing in all the preselected sociodemographic and clinical variables. Table 4-8 shows the odds ratios and 95% confidence intervals for all the baseline variables retained in the final model. Three baseline HRQOL variables were retained in the final model, which were KPS, physical functioning, and vitality. Their associations with primary treatment were similar to those obtained from the previous models. Men with high KPS scores were 1.75 (95% CI: 1.10-2.78) times more likely to receive radical prostatectomy than hormonal therapy. Men with high physical functioning score were 1.62 (95% CI: 1.14-2.31), 1.74 (95% CI: 1.09-2.77), and 2.03 (95% CI: 1.24-3.33) times more likely to receive radical prostatectomy than radiation therapy, expectant management, and hormonal therapy, respectively. Men with high vitality score were

1.49 (95% CI: 1.12-2.00), 1.83 (95% CI: 1.21-2.77) and 2.07 (95% CI: 2.01-1.24-3.27) times more likely to receive radical prostatectomy than the other three treatments, respectively. None of the three retained HRQOL variables were significantly associated with treatments when choosing from radiation therapy, expectant management, or hormonal therapy.

The Confounding Effect of Baseline HRQOL

The associations between definitive treatment, including both radical prostatectomy and radiation therapy, and 10-year all-cause mortality were compared before and after adjustment of the baseline HRQOL variables in addition to comprehensive sociodemographic and clinical variables. Since substantial distinctions were founded between men treated with radical prostatectomy and radiation therapy in part I, radical prostatectomy and radiation therapy were further compared with conservative treatment separately. The associations with 10-year prostate cancer-specific and other cause mortality were also examined to assess the plausibility of the findings.

Descriptive and Univariate Analysis

The final sample included 1,700 men aged 65 years old or above, who were newly diagnosed with low- or intermediate-risk prostate cancer. Out of the entire sample, 611 men received radical prostatectomy, 727 men received radiation therapy, 228 men received expectant management, and 134 men received hormonal therapy. The baseline characteristics distributions and crude associations with primary treatment were similar to the findings in Part I. The missingness on baseline characteristic variables was minor except for KPS. The missing data rate was similar across the groups.

The entire sample was divided into a definitive treatment group and a conservative treatment group, and the baseline characteristics were compared. The definitive treatment group consisted of 1,338 men treated with either radical prostatectomy or radiation therapy. The

conservative treatment group consisted of 362 men treated with either expectant management or hormonal therapy. The mean length of follow-up since diagnosis was similar between the comparison groups, which was 4.4 years. The observed all-cause mortality rate was 13.4% (228 cases) in the entire sample, 10.6% in the definitive treatment group (142 cases), and 23.8% (86 cases) in the conservative treatment group. Most deaths were due to reasons other than prostate cancer. The prostate cancer specific mortality rate was only 1.4% in the entire sample (24 cases), which accounted for 10.5 % all-cause death. The definitive treatment group had a lower prostate cancer-specific mortality rate than the conservative treatment group, which was 1.2% (16 cases) vs. 2.2% (8 cases).

Table 4-9 and Table 4-10 summarize the descriptive statistics for baseline sociodemographic and clinical variables. Their associations with treatment were examined by using logistic regressions after missing data were imputed by using the multiple imputation approach. The definitive treatment was associated with younger age, being married, higher education level, higher annual household income, higher tumor grade, and less comorbidities. Regarding specific disease types, men in the definitive treatment group were less likely to have heart disease, neurological disease/stroke, diabetes, and urinary conditions. Table 4-11 summarizes the descriptive statistics for dichotomized baseline HRQOL variables, and their associations with treatment. Definitive treatment was strongly associated with high SF-36 scores except for mental health. Definitive treatment was also strongly associated with high PCI scores except for urinary function and bowel function.

Table 4-12 and Table 4-13 summarize the results of univariate Cox regression analyses for all baseline sociodemographic and clinical variables. With regard to the sociodemographic variables, older age and current smoker at diagnosis were significantly associated with increased

hazards for all-cause and other-cause mortality. Higher annual household income was significantly associated with decreased hazard for all-cause and other-cause mortalities. Few sociodemographic variables were associated with prostate cancer-specific mortality. Clinical variables that significantly associated with all-cause and other-cause mortality were heart disease, neurological disease/stroke, diabetes, and blood disease. Although not statistically significant, a dose response relationship was observed for the number of comorbidities. The hazards for all-cause and other-cause mortality increased with the number of comorbidities. The only variable that significantly associated with prostate cancer-specific mortality was tumor grade. A higher grade was associated with higher hazard for prostate cancer-specific mortality.

Table 4-16 summarizes the univariate Cox regression analysis results for the baseline HRQOL variables. High scores of KPS and all the eight SF-36 variables were strongly associated with decreased hazards for all-cause and other-cause mortality. High role emotional score was associated with decreased hazard for prostate cancer-specific mortality. With regard to the PCI variables, high scores of bowel bother, sexual function, and sexual bother were significantly associated with decreased hazards for all-cause and other-cause mortality. High urinary bother score was also associated with decreased all-cause mortality. Few baseline PCI variables were associated with prostate cancer-specific mortality.

Propensity Score Comparisons

Two propensity score models were developed separately. The reference model included all the baseline sociodemographic and clinical variables. The HRQOL model included the same set of variables, plus the dichotomized baseline HRQOL variables. Figure 4-1 compares the propensity score distributions for definitive treatment vs. conservative treatment. As expected, the propensity scores for the definitive treatment group were higher than those for the conservative treatment group. The definitive treatment curves were skewed towards 1, while the

conservative treatment curves spread more evenly. There were some overlaps, regardless of the baseline HRQOL consideration. The mean reference propensity to receive definitive treatment in men actually treated definitively was 0.83 (SD=0.15), compared with 0.62 (SD=0.22) in men actually treated conservatively. The two HRQOL curves were slightly further apart after the two reference curves. The mean HRQOL propensity was 0.83 (SD=0.15) vs. 0.61 (SD=0.23). The shifting indicated that the reference model systematically underestimated the propensity discrepancy between the two comparison groups.

Figure 4-2 compares the propensity scores for radical prostatectomy vs. conservative treatment. The propensity to receive radical prostatectomy was very different between these two groups, regardless of the baseline HRQOL consideration. The radical prostatectomy curves were highly skewed towards 1 while the conservative treatment curves were highly skewed towards 0. The overlaps were limited. The mean reference propensity was 0.82 (SD= 0.19) vs. 0.30 (SD=0.30). The HRQOL propensity curves were slightly further apart. The mean propensity was 0.83 (SD=0.19) vs. 0.28 (SD=0.29). Figure 4-3 compared the propensity scores for radiation therapy vs. conservative treatment. Opposite to figure 4-2, the propensity curves were much less skewed, regardless of the baseline HRQOL consideration. The overlaps were moderate. The mean reference propensity was 0.71 (SD=0.15) vs. 0.58 (SD=0.18). The mean HRQOL propensity was 0.72 (SD=0.15) vs. 0.57 (SD=0.19).

Confounding Balance by Propensity Score

Logistic regression models were used to determine whether the baseline characteristics were balanced by propensity score. It was found that all the baseline variables were well balanced by the HRQOL score for all the treatment comparisons. The reference score balanced all the sociodemographic and clinical variables, but not a few baseline HRQOL variables. As shown in Table 4-15, the reference propensity score poorly balanced four SF-36 variables in

either dichotomized or numeric forms between definitive and conservative treatments, which were physical functioning, role-physical, general health, and vitality ($P<0.05$). All the unbalanced HRQOL variables had odds ratios above 1.00, indicating that definitive treatment remained associated with high scores. Table 4-16 shows that more baseline HRQOL variables were unbalanced by the reference score when comparing radical prostatectomy and conservative treatment. Besides the four SF-36 variables mentioned above, the unbalanced variables include numeric KPS, dichotomized bodily pain, and numeric sexual function. Table 4-17 shows that the HRQOL variables were much better balanced by the reference score when comparing radiation therapy and conservative treatment. The only unbalance variables were role-physical in both dichotomized and numeric forms, and numeric general health.

Propensity Score Quintile Specific Hazard Ratios

Table 4-18 and Table 4-19 show the propensity score quintile specific hazard ratios for all-cause mortality. The hazard ratios were consistently below 1.00 when comparing definitive treatment and radiation therapy vs. conservative treatment. Heterogeneity was observed when comparing radical prostatectomy vs. conservative treatment. The first quintile hazard ratios were above 1.00 while the hazard ratios in the other quintiles were below 1.00. It indicated that the survival benefit of radical prostatectomy was modified by propensity score.

Confounding Effect of Baseline HRQOL

Cox proportional hazard model was used to compare the 10-year mortality outcomes between definitive and the conservative treatment. Radical prostatectomy and radiation therapy were also compared with conservative treatment separately. The log-log curves for each treatment comparison are presented from Figure 4-4 to Figure 4-6. The curves were parallel to each other for all the three mortality outcomes. The proportional hazard assumptions were satisfied. Potential bias due to non-random censoring was controlled by using the IPCW method

as described in the methodology section. The results obtained by different confounding adjustment methods are summarized in Table 4-20 to Table 4-22. The adjusted hazard ratios for 10-year all-cause mortality are also summarized from Figure 4-7 to Figure 4-9.

Definitive treatment vs. conservative treatment

The crude hazard ratio was 0.35 (95% CI: 0.16 – 0.77), indicating strong association between definitive treatment and longer survival. The hazard ratio increased toward 1.00 after adjusting for baseline sociodemographic and clinical variables, and further increased slightly after additional HRQOL adjustment. All confounding adjustment methods yielded similar results. Before and after the HRQOL consideration, the adjusted hazard ratio was 0.44 (95% CI: 0.19-1.05) vs. 0.46 (95% CI: 0.19-1.08) when adjusting the continuous propensity score; 0.43 (95% CI: 0.19-0.91) vs. 0.48 (95% CI: 0.23-1.00) when adjusting the propensity score quintiles; 0.43 (95% CI: 0.19-0.96) vs. 0.46 (95% CI: 0.20 0-1.04) when weighting to the entire sample; 0.42 (95% CI: 0.18-0.97) vs. 0.44 (95% CI: 0.19-1.05) when weighting to the definitive treatment group, and 0.50 (95% CI: 0. 24-1.05) vs. 0.51 (95% CI: .0.24-1.09) when weighting to the conservative treatment group. The relative changes in hazard ratio ranged from 1.9% to 9.3%. The absolute changes were minor, ranging from 0.01 to 0.04. The confounding effect is not significant.

We separately compared the prostate cancer-specific mortality and other-cause mortality, looking for clues of unmeasured confounding. The crude hazard ratio for prostate cancer-specific mortality was 0.30 (95% CI: 0.08-1.07). The hazard ratio ranged from 0.19 to 0.35 after the baseline sociodemographic and clinical variables were adjusted, depending on the confounding adjustment method used. Additional HRQOL adjustment further increased the hazard ratios slightly. The relative changes ranged from 1.4% to 4.4%. The absolute differences were less than 0.02. The hazard ratios for other-cause mortality had values close to those for all-cause mortality

since it accounted for 90% all-cause deaths. The crude hazard ratio was 0.36 (95% CI: 0.16-0.79). The hazard ratios obtained from different methods were similar, ranging from 0.46 – 0.52 after adjusting the baseline sociodemographic and clinical factors. Additional HRQOL adjustment slightly increased the hazard ratios more towards 1.00. The relative changes ranged from 1.8% to 10.2%, and the absolute changes ranged from 0.01 to 0.05. The adjusted hazard ratios for other-cause mortality were more close to 1.00 than those for prostate cancer-specific mortality, regardless of the confounding adjustment method used.

The results above indicated that definitive treatment was strongly associated with all-cause survival benefit relative to conservative treatment. Although attenuated, the association remained strong after confounding adjustment. Additional HRQOL adjustment had small impact. The relative changes were less than 10%, regardless of the confounding adjustment method used. The variation in hazard ratio resulting from different methods was small. The strength of the association between definitive treatment and survival was stronger for prostate cancer death than other-cause death, which was plausible. Nevertheless, it was still questionable that definitive treatment for prostate cancer could reduce the hazard for other-cause death for nearly 50%. Figure 4-10 presented the crude and weighted survival curves for 10-year all-cause mortality. The gap between the definitive treatment and conservative treatment curves became slightly narrower after the baseline HRQOL variables were adjusted additionally.

Radical prostatectomy vs. conservative treatment

The crude hazard ratio for all-cause mortality was 0.27 (95% CI: 0.12-0.64). All hazard ratios were below 1.00 after adjustment of baseline sociodemographic and clinical variables. Additional HRQOL adjustment greatly increased all hazard ratios for 20-30%, depending on the method used. The absolute changes ranged from 0.08 to 0.24. Different confounding adjustment methods produced somewhat different estimates. When weighting to the radical prostatectomy

group, the hazard ratio was 0.36 (95% CI: 0.11-1.16) vs. 0.45 (0.13-1.51) before and after additional HRQOL adjustment. Similar hazard ratios were obtained when using the propensity score adjustment. Higher hazard ratio was obtained when weighting to the entire sample, which was 0.57 (95% CI: 0.18-2.78) vs. 0.81 (95% CI: 0.23-2.81) before and after additional HRQOL adjustment. The highest hazard ratio was obtained when weighting to the conservative treatment group, which was 0.83 (95% CI: 0.18 – 3.85) and 1.03 (94% CI: 0.21-5.19) before and after additional HRQOL adjustment.

The crude hazard ratio for prostate cancer-specific mortality was 0.19 (95% CI: 0.01-3.93). The hazard ratios ranged from 0.12 to 0.29 after adjusting for the baseline sociodemographic and clinical variables. The prostate cancer survival benefit was further strengthened after additional HRQOL adjustment as all hazard ratios decreased further away from 1.00. Although the relative changes appeared to be substantial, the absolute changes were minor ranging from -0.03 to -0.06. The crude hazard ratio for other-cause mortality was 0.28 (95% CI: 0.11-0.69). The adjusted hazard ratios from different methods had the same pattern with those for all-cause mortality. All hazard ratios remained below 1.00 after adjusting for baseline sociodemographic and clinical variables. Additional HRQOL adjustment significantly increased all hazard ratios for 20% - 30%. Radical prostatectomy associated other-cause survival benefit diminished when weighting to the conservative treatment group. The association between radical prostatectomy and survival was stronger for prostate cancer-specific death than other-cause death, regardless of the confounding adjustment method used.

The results above indicated that the baseline HRQOL variables confounded the association between radical prostatectomy and all-cause mortality. Radical prostatectomy associated survival benefit was overestimated for approximately 20-30%, depending on the confounding adjustment

method used. The overestimation seemed owing to the overestimated other-cause survival but not prostate cancer-specific survival. It was also noticed that different confounding adjustment methods yielded different estimates. After additional adjustment of the baseline HRQOL variables, the all-cause survival benefit disappeared when weighting to the conservative treatment group (hazard ratio: 1.03, 95% CI: 0.21-5.19), but remained strong when weighting to the radical prostatectomy group (hazard ratio: 0.45, 95% CI: 0.13-1.51). The results revealed that the treatment effect varied in the different target populations. Radical prostatectomy might prolong survival in the population represented by the radical prostatectomy group, but might not in the population represented by the conservative treatment group. Figure 4-11 presents the crude and weighted survival curves. The gap between the two treatment curves were narrower after the baseline HRQOL variables were adjusted additionally.

Radiation therapy vs. conservative treatment

The crude hazard ratio was 0.43 (95% CI: 0.20-0.95). All confounding adjustment methods yielded very similar estimates after adjusting for baseline sociodemographic and clinical variables, which ranged from 0.47 to 0.50. Additional HRQOL adjustment had little impacts. All hazard ratios remained nearly unchanged. The relative differences were less than 2% and the absolute differences were equal or less than 0.01.

The crude hazard ratio for prostate cancer mortality was 0.38 (95% CI: 0.10-1.42). The hazard ratio ranged from 0.24 to 0.41, adjusting for the baseline sociodemographic and clinical variables. Additional HRQOL adjustment had minor impacts. The relative changes were less than 7.1% and the absolute changes were less than 0.03. The crude hazard ratio for other-cause mortality was 0.43 (95% CI: 0.19-1.00). The hazard ratio ranged from 0.47 to 0.52, adjusting for the baseline sociodemographic and clinical variables. Additional HRQOL adjustment had little

impact. The adjusted hazard ratios for other-cause mortality were closer to 1.00 than those for prostate cancer-specific mortality, regardless of the confounding adjustment method used.

The results indicated that the baseline HRQOL variables did not confound the association between radiation therapy and all-cause mortality. Additional adjustment of HRQOL had little impact on the estimates. The strength of the association between radiation therapy and survival was stronger for prostate cancer death than other-cause death, which was plausible. Nevertheless, it was questionable that radiation therapy could reduce other-cause mortality for nearly 50%. Figure 4-13 presents the crude and weighted survival curves. The gap between the two treatment curves nearly unchanged after the baseline HRQOL variables were considered additionally

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Table 4-1. Baseline sociodemographic variable distributions in CaPSURE elderly men with localized prostate cancer

		Overall, n (%) (N=1,924)		RP, n (%) (N=676)		RT, n (%) (N=815)		EM, n (%) (N=261)		HT, n (%) (N=172)	
Age	Mean (SD), y		72 (5)		69 (3)		72 (5)		75 (5)		76 (6)
	Median (IQR), y		71 (68-75)		68 (66-70)		73 (69-76)		75 (71-79)		76 (71-80)
	65-67	446	(23.2)	279	(41.3)	132	(16.2)	23	(8.8)	12	(7.0)
	68-70	475	(24.7)	243	(35.9)	179	(22.0)	32	(12.3)	21	(12.2)
	71-73	327	(17.0)	108	(16.0)	156	(19.1)	38	(14.6)	25	(14.5)
	74-76	310	(16.1)	34	(5.0)	187	(22.9)	59	(22.6)	30	(17.4)
	>=77	366	(19.0)	12	(1.8)	161	(19.8)	109	(41.8)	84	(48.8)
Race	White	1752	(91.1)	628	(92.9)	745	(91.4)	227	(87.0)	152	(88.4)
	Other	128	(6.7)	41	(6.1)	53	(6.5)	16	(6.1)	18	(10.5)
	Missing	44	(2.3)	7	(1.0)	17	(2.1)	18	(6.9)	2	(1.2)
Marital status	Married	1612	(83.8)	612	(90.5)	681	(83.6)	192	(73.6)	127	(73.8)
	Single	256	(13.3)	55	(8.1)	110	(13.5)	52	(19.9)	39	(22.7)
	Missing	56	(2.9)	9	(1.3)	24	(2.9)	17	(6.5)	6	(3.5)
Education	<HS	305	(15.9)	75	(11.1)	139	(17.1)	57	(21.8)	34	(19.8)
	HS / SC	872	(45.3)	297	(43.9)	369	(45.3)	120	(46.0)	86	(50.0)
	≥College	693	(36.0)	295	(43.6)	282	(34.6)	67	(25.7)	49	(28.5)
	Missing	54	(2.8)	9	(1.3)	25	(3.1)	17	(6.5)	3	(1.7)
Annual house hold Income	<20K	270	(14.0)	61	(9.0)	130	(16.0)	47	(18.0)	32	(18.6)
	20K-50K	816	(42.4)	277	(41.0)	365	(44.8)	104	(39.8)	70	(40.7)
	>50K	588	(30.6)	272	(40.2)	215	(26.4)	54	(20.7)	47	(27.3)
	Missing	250	(13.0)	66	(9.8)	105	(12.9)	56	(21.5)	23	(13.4)
Insurance	Medicare	1505	(78.2)	551	(81.5)	625	(76.7)	202	(77.4)	127	(73.8)
	Other	355	(18.5)	103	(15.2)	172	(21.1)	45	(17.2)	35	(20.3)
	Missing	64	(3.3)	22	(3.3)	18	(2.2)	14	(5.4)	10	(5.8)
Smoking status	Current	117	(6.1)	46	(6.8)	46	(5.6)	11	(4.2)	14	(8.1)
	Not current	1746	(90.7)	618	(91.4)	742	(91.0)	230	(88.1)	156	(90.7)
	Missing	61	(3.2)	12	(1.8)	27	(3.3)	20	(7.7)	2	(1.2)
Diagnosis year	1995-2000	607	(31.5)	173	(25.6)	273	(33.5)	100	(38.3)	61	(35.5)
	2001-2007	1317	(68.5)	503	(74.4)	542	(66.5)	161	(61.7)	111	(64.5)

Table 4-2. Baseline clinical variable distributions in CaPSURE elderly men with localized prostate cancer

		Overall, n (%) (N=1,924)		RP, n (%) (N=676)		RT, n (%) (N=815)		EM, n (%) (N=261)		HT, n (%) (N=172)	
Cancer risk	Low	778	(40.4)	277	(41.0)	320	(39.3)	137	(52.5)	44	(25.6)
	Intermediate	794	(41.3)	294	(43.5)	362	(44.4)	64	(24.5)	74	(43.0)
	High	255	(13.3)	72	(10.7)	109	(13.4)	26	(10.0)	48	(27.9)
	Missing	97	(5.0)	33	(4.9)	24	(2.9)	34	(13.0)	6	(3.5)
BMI	<25	558	(29.0)	174	(25.7)	232	(28.5)	95	(36.4)	57	(33.1)
	25-29.9	923	(48.0)	349	(51.6)	396	(48.6)	105	(40.2)	73	(42.4)
	>=30	369	(19.2)	138	(20.4)	156	(19.1)	39	(14.9)	36	(20.9)
	Missing	74	(3.8)	15	(2.2)	31	(3.8)	22	(8.4)	6	(3.5)
Heart disease	Yes	533	(27.7)	117	(17.3)	265	(32.5)	87	(33.3)	64	(37.2)
	No	1340	(69.6)	549	(81.2)	532	(65.3)	156	(59.8)	103	(59.9)
	Missing	51	(2.7)	10	(1.5)	18	(2.2)	18	(6.9)	5	(2.9)
Neurologic disease/stroke	Yes	158	(8.2)	31	(4.6)	76	(9.3)	28	(10.7)	23	(13.4)
	No	1715	(89.1)	635	(93.9)	721	(88.5)	215	(82.4)	144	(83.7)
	Missing	51	(2.7)	10	(1.5)	18	(2.2)	18	(6.9)	5	(2.9)
Other cancer	Yes	312	(16.2)	94	(13.9)	146	(17.9)	36	(13.8)	36	(20.9)
	No	1561	(81.1)	572	(84.6)	651	(79.9)	207	(79.3)	131	(76.2)
	Missing	51	(2.7)	10	(1.5)	18	(2.2)	18	(6.9)	5	(2.9)
Diabetes	Yes	235	(12.2)	60	(8.9)	99	(12.1)	41	(15.7)	35	(20.3)
	No	1638	(85.1)	606	(89.6)	698	(85.6)	202	(77.4)	132	(76.7)
	Missing	51	(2.7)	10	(1.5)	18	(2.2)	18	(6.9)	5	(2.9)
Kidney disease	Yes	104	(5.4)	35	(5.2)	41	(5.0)	24	(9.2)	4	(2.3)
	No	1769	(91.9)	631	(93.3)	756	(92.8)	219	(83.9)	163	(94.8)
	Missing	51	(2.7)	10	(1.5)	18	(2.2)	18	(6.9)	5	(2.9)
Hypertension	Yes	957	(49.7)	302	(44.7)	434	(53.3)	122	(46.7)	99	(57.6)
	No	916	(47.6)	364	(53.8)	363	(44.5)	121	(46.4)	68	(39.5)
	Missing	51	(2.7)	10	(1.5)	18	(2.2)	18	(6.9)	5	(2.9)

Table 4-2.Continued

		Overall, n (%) (N=1,924)		RP, n (%) (N=676)		RT, n (%) (N=815)		EM, n (%) (N=261)		HT, n (%) (N=172)	
Arthritis	Yes	865	(45.0)	290	(42.9)	382	(46.9)	111	(42.5)	82	(47.7)
	No	1008	(52.4)	376	(55.6)	415	(50.9)	132	(50.6)	85	(49.4)
	Missing	51	(2.7)	10	(1.5)	18	(2.2)	18	(6.9)	5	(2.9)
Blood disease	Yes	48	(2.5)	12	(1.8)	26	(3.2)	4	(1.5)	6	(3.5)
	No	1825	(94.9)	654	(96.7)	771	(94.6)	239	(91.6)	161	(93.6)
	Missing	51	(2.7)	10	(1.5)	18	(2.2)	18	(6.9)	5	(2.9)
GI disease	Yes	302	(15.7)	105	(15.5)	123	(15.1)	47	(18.0)	27	(15.7)
	No	1571	(81.7)	561	(83.0)	674	(82.7)	196	(75.1)	140	(81.4)
	Missing	51	(2.7)	10	(1.5)	18	(2.2)	18	(6.9)	5	(2.9)
Lung disease	Yes	181	(9.4)	47	(7.0)	84	(10.3)	35	(13.4)	15	(8.7)
	No	1692	(87.9)	619	(91.6)	713	(87.5)	208	(79.7)	152	(88.4)
	Missing	51	(2.7)	10	(1.5)	18	(2.2)	18	(6.9)	5	(2.9)
Urinary condition	Yes	359	(18.7)	119	(17.6)	141	(17.3)	50	(19.2)	49	(28.5)
	No	1514	(78.7)	547	(80.9)	656	(80.5)	193	(73.9)	118	(68.6)
	Missing	51	(2.7)	10	(1.5)	18	(2.2)	18	(6.9)	5	(2.9)
Other disease	0	140	(7.3)	52	(7.7)	62	(7.6)	11	(4.2)	15	(8.7)
	≥1	1733	(90.1)	614	(90.8)	735	(90.2)	232	(88.9)	152	(88.4)
	Missing	51	(2.7)	10	(1.5)	18	(2.2)	18	(6.9)	5	(2.9)
Total number of comorbidity	0	169	(8.8)	83	(12.3)	56	(6.9)	16	(6.1)	14	(8.1)
	1	461	(24.0)	198	(29.3)	185	(22.7)	54	(20.7)	24	(14.0)
	2	535	(27.8)	197	(29.1)	238	(29.2)	66	(25.3)	34	(19.8)
	≥3	708	(36.8)	188	(27.8)	318	(39.0)	107	(41.0)	95	(55.2)
	Missing	51	(2.7)	10	(1.5)	18	(2.2)	18	(6.9)	5	(2.9)

Table 4-3. Baseline HRQOL variable distributions in CaPSURE elderly men with localized prostate cancer

		Overall, n (%) (N=1,924)	RP, n (%) (N=676)	RT, n (%) (N=815)	EM, n (%) (N=261)	HT, n (%) (N=172)
KPS	Mean (SD)	98 (5)	99 (4)	97 (6)	98 (4)	95 (7)
	Median (IQR)	100 (100-100)	100 (100-100)	100 (100-100)	100 (100-100)	100 (90-100)
	High score	535 (27.8)	184 (27.2)	213 (26.1)	90 (34.5)	48 (27.9)
	Low score	134 (7.0)	21 (3.1)	66 (8.1)	18 (6.9)	29 (16.9)
	Missing	1255 (65.2)	471 (69.7)	536 (65.8)	153 (58.6)	95 (55.2)
SF-36						
PF	Mean (SD)	81 (22)	88 (16)	79 (23)	75 (25)	71 (26)
	Median (IQR)	90 (75-100)	95 (85-100)	90 (70-95)	80 (61-95)	80 (55-90)
	High score	1418 (73.7)	586 (86.7)	570 (69.9)	167 (64.0)	95 (55.2)
	Low score	462 (24.0)	78 (11.5)	223 (27.4)	91 (34.9)	70 (40.7)
	Missing	44 (2.3)	12 (1.8)	22 (2.7)	3 (1.1)	7 (4.1)
RP	Mean (SD)	74 (38)	83 (32)	72 (38)	64 (41)	62 (43)
	Median (IQR)	100 (50-100)	100 (75-100)	100 (50-100)	75 (25-100)	75 (25-100)
	High score	1322 (68.7)	539 (79.7)	542 (66.5)	146 (55.9)	95 (55.2)
	Low score	564 (29.3)	127 (18.8)	256 (31.4)	111 (42.5)	70 (40.7)
	Missing	38 (2.0)	10 (1.5)	17 (2.1)	4 (1.5)	7 (4.1)
BP	Mean (SD)	82 (21)	86 (19)	82 (21)	79 (22)	78 (23)
	Median (IQR)	90 (68-100)	90 (78-100)	90 (68-100)	90 (68-100)	90 (58-100)
	High score	1366 (71.0)	526 (77.8)	569 (69.8)	165 (63.2)	106 (61.6)
	Low score	523 (27.2)	142 (21.0)	230 (28.2)	88 (33.7)	63 (36.6)
	Missing	35 (1.8)	8 (1.2)	16 (2.0)	8 (3.1)	3 (1.7)
GH	Mean (SD)	71 (19)	76 (17)	70 (20)	66 (21)	64 (21)
	Median (IQR)	75 (60-85)	80 (65-90)	75 (60-85)	70 (50-80)	70 (45-80)
	High score	1353 (70.3)	547 (80.9)	553 (67.9)	157 (60.2)	96 (55.8)
	Low score	528 (27.4)	120 (17.8)	242 (29.7)	95 (36.4)	71 (41.3)
	Missing	43 (2.2)	9 (1.3)	20 (2.5)	9 (3.4)	5 (2.9)

Table 4-3.Continued

		Overall, n (%) (N=1,924)	RP, n (%) (N=676)	RT, n (%) (N=815)	EM, n (%) (N=261)	HT, n (%) (N=172)
RE	Mean (SD)	84 (32)	89 (26)	83 (33)	80 (34)	79 (37)
	Median (IQR)	100 (100-100)	100 (100-100)	100 (83-100)	100 (67-100)	100 (67-100)
	High score	1440 (74.8)	545 (80.6)	600 (73.6)	177 (67.8)	118 (68.6)
	Low score	444 (23.1)	119 (17.6)	200 (24.5)	78 (29.9)	47 (27.3)
	Missing	40 (2.1)	12 (1.8)	15 (1.8)	6 (2.3)	7 (4.1)
VT	Mean (SD)	66 (19)	70 (18)	65 (20)	62 (19)	59 (21)
	Median (IQR)	70 (50-80)	75 (60-85)	70 (50-80)	60 (50-75)	60 (45-75)
	High score	1282 (66.6)	525 (77.7)	520 (63.8)	149 (57.1)	88 (51.2)
	Low score	616 (32.0)	145 (21.4)	283 (34.7)	109 (41.8)	79 (45.9)
	Missing	26 (1.4)	6 (0.9)	12 (1.5)	3 (1.1)	5 (2.9)
SO	Mean (SD)	88 (19)	91 (17)	88 (19)	86 (21)	84 (23)
	Median (IQR)	100 (75-100)	100 (88-100)	100 (75-100)	100 (75-100)	100 (75-100)
	High score	1205 (62.6)	463 (68.5)	500 (61.3)	150 (57.5)	92 (53.5)
	Low score	674 (35.0)	201 (29.7)	294 (36.1)	103 (39.5)	76 (44.2)
	Missing	45 (2.3)	12 (1.8)	21 (2.6)	8 (3.1)	4 (2.3)
MH	Mean (SD)	81 (15)	82 (15)	80 (15)	81 (15)	79 (17)
	Median (IQR)	84 (72-92)	84 (76-92)	84 (72-92)	84 (72-92)	84 (72-92)
	High score	1078 (56.0)	409 (60.5)	436 (53.5)	144 (55.2)	89 (51.7)
	Low score	817 (42.5)	261 (38.6)	365 (44.8)	114 (43.7)	77 (44.8)
	Missing	29 (1.5)	6 (0.9)	14 (1.7)	3 (1.1)	6 (3.5)
UCLA-PCI UF	Mean (SD)	91 (14)	92 (13)	91 (13)	88 (18)	88 (17)
	Median (IQR)	100 (82-100)	100 (87-100)	100 (83-100)	100 (80-100)	100 (80-100)
	High score	1108 (57.6)	415 (61.4)	457 (56.1)	147 (56.3)	89 (51.7)
	Low score	772 (40.1)	249 (36.8)	336 (41.2)	112 (42.9)	75 (43.6)
	Missing	44 (2.3)	12 (1.8)	22 (2.7)	2 (0.8)	8 (4.7)

Table 4-3.Continued

		Overall, n (%) (N=1,924)	RP, n (%) (N=676)	RT, n (%) (N=815)	EM, n (%) (N=261)	HT, n (%) (N=172)
UB	Mean (SD)	81 (26)	84 (24)	81 (26)	78 (28)	76 (30)
	Median (IQR)	100 (75-100)	100 (75-100)	100 (75-100)	100 (75-100)	100 (50-100)
	High score	1061 (55.1)	398 (58.9)	450 (55.2)	131 (50.2)	82 (47.7)
	Low score	821 (42.7)	267 (39.5)	346 (42.5)	127 (48.7)	81 (47.1)
	Missing	42 (2.2)	11 (1.6)	19 (2.3)	3 (1.1)	9 (5.2)
BF	Mean (SD)	87 (14)	89 (14)	87 (14)	87 (15)	84 (17)
	Median (IQR)	94 (81-100)	94 (85-100)	94 (80-95)	94 (81-100)	89 (75-94)
	High score	1085 (56.4)	448 (55.0)	448 (55.0)	140 (53.6)	79 (45.9)
	Low score	826 (42.9)	359 (44.0)	359 (44.0)	117 (44.8)	92 (53.5)
	Missing	13 (0.7)	8 (1.0)	8 (1.0)	4 (1.5)	1 (0.6)
BB	Mean (SD)	87 (22)	90 (19)	86 (22)	85 (22)	80 (27)
	Median (IQR)	100 (75-100)	100 (75-100)	100 (75-100)	100 (75-100)	100 (75-100)
	High score	1278 (66.4)	497 (73.5)	528 (64.8)	157 (60.2)	96 (55.8)
	Low score	623 (32.4)	175 (25.9)	272 (33.4)	101 (38.7)	75 (43.6)
	Missing	23 (1.2)	4 (0.6)	15 (1.8)	3 (1.1)	1 (0.6)
SF	Mean (SD)	41 (28)	49 (28)	38 (28)	37 (27)	28 (24)
	Median (IQR)	40 (17-66)	53 (27-75)	35 (14-61)	32 (10-61)	24 (7-46)
	High score	868 (45.1)	389 (57.5)	332 (40.7)	102 (39.1)	45 (26.2)
	Low score	997 (51.8)	273 (40.4)	455 (55.8)	149 (57.1)	120 (69.8)
	Missing	59 (3.1)	14 (2.1)	28 (3.4)	10 (3.8)	7 (4.1)
SB	Mean (SD)	54 (39)	59 (37)	52 (39)	48 (40)	51 (42)
	Median (IQR)	50 (25-100)	75 (25-100)	50 (0-100)	50 (0-100)	50 (0-100)
	High score	1097 (57.0)	434 (64.2)	450 (55.2)	126 (48.3)	87 (50.6)
	Low score	712 (37.0)	214 (31.7)	315 (38.7)	115 (44.1)	68 (39.5)
	Missing	115 (6.0)	28 (4.1)	50 (6.1)	20 (7.7)	17 (9.9)

Table 4-4. Crude estimates of associations between baseline sociodemographic variables and primary treatment (odds ratios and 95% confidence intervals)

		RP vs. RT	RP vs. EM	RP vs. HT
Age	65-67 (ref)	1.00	1.00	1.00
	68-70	0.70 (0.52, 0.95)*	0.49 (0.32, 0.75) ***	0.50 (0.24, 1.03)
	71-73	0.33 (0.24, 0.47)***	0.25 (0.16, 0.39) ***	0.21 (0.10, 0.44) ***
	74-76	0.09 (0.06, 0.14) ***	0.05 (0.03, 0.09) ***	0.05 (0.02, 0.11) ***
	≥ 77	0.04 (0.02, 0.07) ***	0.01 (0.01, 0.03) ***	0.01 (0.00, 0.02) ***
Race	Other races (ref)	1.00	1.00	1.00
	White	1.11 (0.72, 1.69)	1.06 (0.54, 2.13)	1.82 (1.02, 3.33)*
Marital status	Single (ref)	1.00	1.00	1.00
	Married	1.79 (1.27, 2.50)**	3.03 (1.96, 4.55)***	3.45 (2.22, 5.56)***
Education	<HS (ref)	1.00	1.00	1.00
	HS/some College	1.52 (1.10, 2.08)*	1.96 (1.32, 2.94)**	1.56 (0.98, 2.50)
	≥College	1.96 (1.43, 2.70)***	3.45 (2.22, 5.26)***	2.70 (1.64, 4.55)***
Income	<20K (ref)	1.00	1.00	1.00
	20K-50K	1.61 (1.16, 2.27)**	2.13 (1.39, 3.23)**	2.08 (1.20, 3.70)**
	>50K	2.70 (1.92, 3.85)***	3.85 (2.38, 5.88)***	2.94 (1.75, 5.00)***
Insurance	Other ins (ref)	1.00	1.00	1.00
	Medicare	1.49 (1.14, 1.96)**	1.22 (0.83, 1.79)	1.52 (0.94, 2.44)
Smoke	Not current (ref)	1.00	1.00	1.00
	Current smoker	1.18 (0.77, 1.79)	1.64 (0.82, 3.23)	0.84 (0.45, 1.56)
Diagnosis year	1995-2000 (ref)	1.00	1.00	1.00
	2001-2007	1.49 (1.19, 1.89)**	1.54 (1.18, 2.00) **	1.59 (1.09, 2.27)*

*P<0.05; **P<0.01; ***P<0.001;

Table 4-4.Continued

		RT Vs. EM	RT vs. HT	EM vs. HT
Age	65-67 (ref)	1.00	1.00	1.00
	68-70	0.69 (0.44, 1.10)	0.71 (0.33, 1.49)	1.02 (0.45, 2.27)
	71-73	0.74 (0.46, 1.18)	0.63 (0.30, 1.32)	0.85 (0.38, 1.92)
	74-76	0.58 (0.37, 0.90)*	0.55 (0.27, 1.12)	0.95 (0.44, 2.04)
	≥ 77	0.39 (0.26, 0.60) ***	0.20 (0.1, 0.38) ***	0.51 (0.25, 1.02)
Race	Other races (ref)	1.00	1.00	1.00
	White	0.96 (0.50, 1.85)	1.64 (0.94, 2.94)	1.72 (0.81, 3.70)
Marital status	Single (ref)	1.00	1.00	1.00
	Married	1.69 (1.16, 2.50)**	1.96 (1.3, 2.94)**	1.15 (0.72, 1.85)
Education	<HS (ref)	1.00	1.00	1.00
	HS/SC	1.30 (0.90, 1.85)	1.04 (0.67, 1.64)	0.81 (0.48, 1.33)
	≥College	1.72 (1.16, 2.56)**	1.37 (0.85, 2.22)	0.80 (0.46, 1.39)
Income	<20K (ref)	1.00	1.00	1.00
	20K-50K	1.30 (0.88, 1.92)	1.30 (0.77, 2.17)	0.99 (0.57, 1.72)
	>50K	1.39 (0.90, 2.17)	1.09 (0.65, 1.85)	0.78 (0.45, 1.37)
Insurance	Other ins (ref)	1.00	1.00	1.00
	Medicare	0.82 (0.57, 1.18)	1.01 (0.63, 1.61)	1.23 (0.71, 2.13)
Smoke	Not current (ref)	1.00	1.00	1.00
	Current smoker	1.39 (0.68, 2.86)	0.71 (0.38, 1.33)	0.51 (0.22, 1.19)
Diagnosis year	1995-2000 (ref)	1.00	1.00	1.00
	2001-2007	1.02 (0.79, 1.32)	1.05 (0.73, 1.52)	1.03 (0.70, 1.52)

*P<0.05; **P<0.01; ***P<0.001;

Table 4-5. Crude estimates of associations between baseline clinical variables and primary treatment (odds ratios and 95% confidence intervals)

		RP vs. RT	RP vs. EM	RP vs. HT
Cancer risk	Low (ref)	1.00	1.00	1.00
	Intermediate	0.93 (0.75, 1.16)	2.27 (1.64, 3.23)***	0.67 (0.44, 1.02)
	high	0.74 (0.53, 1.04)	1.41 (0.85, 2.33)	0.24 (0.15, 0.39)***
BMI	<25 (ref)	1.00	1.00	1.00
	25-29.9	1.19 (0.94, 1.52)	1.75 (1.25, 2.50)**	1.59 (1.08, 2.33)*
	>=30	1.19 (0.88, 1.61)	1.92 (1.23, 3.03)**	1.32 (0.82, 2.13)
Total number of comorbidities	0 (ref)	1.00	1.00	1.00
	1	0.74 (0.50, 1.09)	0.75 (0.41, 1.35)	1.39 (0.68, 2.78)
	2	0.56 (0.38, 0.83)**	0.61 (0.33, 1.10)	0.95 (0.49, 1.89)
	3 or more	0.40 (0.28, 0.60)***	0.35 (0.20, 0.63)***	0.33 (0.18, 0.62)***
Heart disease	Yes vs. no (ref)	0.43 (0.33, 0.55)***	0.38 (0.28, 0.53)***	0.34 (0.24, 0.49)***
Neurological disease/stroke	Yes vs. no (ref)	0.46 (0.30, 0.71)**	0.37 (0.22, 0.63)***	0.3 (0.17, 0.53)***
Other cancer	Yes vs. no (ref)	0.72 (0.55, 0.96)*	0.94 (0.60, 1.47)	0.59 (0.38, 0.90)*
Diabetes	Yes vs. no (ref)	0.69 (0.50, 0.98)*	0.48 (0.31, 0.76)**	0.37 (0.23, 0.58)***
Kidney disease	Yes vs. no (ref)	1.01 (0.64, 1.61)	0.52 (0.30, 0.88)*	2.22 (0.79, 6.25)
Hypertension	Yes vs. no (ref)	0.69 (0.56, 0.85)**	0.83 (0.62, 1.11)	0.58 (0.41, 0.82)**
Arthritis	Yes vs. no (ref)	0.84 (0.68, 1.03)	0.93 (0.70, 1.27)	0.83 (0.58, 1.16)
Blood disease	Yes vs. no (ref)	0.52 (0.26, 1.06)	0.99 (0.30, 3.23)	0.47 (0.17, 1.28)
GI disease	Yes vs. no (ref)	1.03 (0.77, 1.37)	0.76 (0.52, 1.11)	0.99 (0.61, 1.59)
Lung disease	Yes vs. no (ref)	0.64 (0.44, 0.93)*	0.45 (0.28, 0.71)**	0.79 (0.43, 1.45)
Urinary condition	Yes vs. no (ref)	1.01 (0.78, 1.33)	0.88 (0.61, 1.27)	0.54 (0.36, 0.79)**
Other disease	Yes vs. no (ref)	1.01 (0.68, 1.49)	1.75 (0.93, 3.33)	0.83 (0.46, 1.52)

*P<0.05; **P<0.01; ***P<0.001;

Table 4-5. Continued

		RT Vs. EM	RT vs. HT	EM vs. HT
Cancer risk	Low (ref)	1.00	1.00	1.00
	Intermediate	2.44 (1.75, 3.45)***	0.71 (0.47, 1.09)	0.29 (0.18, 0.49)***
	high	1.89 (1.18, 3.03)**	0.33 (0.21, 0.52)***	0.17 (0.09, 0.31)***
BMI	<25 (ref)	1.00	1.00	1.00
	25-29.9	1.47 (1.06, 2.04)*	1.32 (0.91, 1.92)	0.89 (0.57, 1.41)
	>=30	1.64 (1.06, 2.50)*	1.11 (0.70, 1.75)	0.68 (0.39, 1.19)
Number of comorbidities	0 (ref)	1.00	1.00	1.00
	1	1.01 (0.55, 1.89)	1.89 (0.92, 3.85)	1.85 (0.79, 4.35)
	2	1.08 (0.58, 1.96)	1.69 (0.85, 3.33)	1.59 (0.70, 3.57)
	3 or more	0.87 (0.49, 1.56)	0.82 (0.44, 1.54)	0.94 (0.44, 2.00)
Heart disease	Yes vs. no (ref)	0.90 (0.67, 1.22)	0.8 (0.57, 1.12)	0.88 (0.59, 1.33)
Neurological disease/stroke	Yes vs. no (ref)	0.81 (0.51, 1.28)	0.65 (0.40, 1.06)	0.81 (0.45, 1.45)
Other cancer	Yes vs. no (ref)	1.30 (0.86, 1.96)	0.81 (0.54, 1.22)	0.63 (0.37, 1.06)
Diabetes	Yes vs. no (ref)	0.69 (0.46, 1.04)	0.53 (0.35, 0.81)**	0.76 (0.45, 1.27)
Kidney disease	Yes vs. no (ref)	0.51 (0.30, 0.86)*	2.22 (0.79, 6.25)	4.35 (1.47, 12.50)**
Hypertension	Yes vs. no (ref)	1.20 (0.91, 1.61)	0.84 (0.60, 1.19)	0.70 (0.47, 1.03)
Arthritis	Yes vs. no (ref)	1.12 (0.84, 1.49)	0.98 (0.70, 1.37)	0.88 (0.59, 1.30)
Blood disease	Yes vs. no (ref)	1.89 (0.66, 5.56)	0.90 (0.37, 2.22)	0.47 (0.13, 1.69)
GI disease	Yes vs. no (ref)	0.75 (0.51, 1.09)	0.96 (0.60, 1.52)	1.28 (0.74, 2.22)
Lung disease	Yes vs. no (ref)	0.70 (0.46, 1.06)	1.23 (0.69, 2.17)	1.75 (0.93, 3.33)
Urinary condition	Yes vs. no (ref)	0.86 (0.60, 1.23)	0.53 (0.36, 0.78)**	0.61 (0.39, 0.96)*
Other disease	Yes vs. no (ref)	1.75 (0.93, 3.33)	0.83 (0.46, 1.49)	0.47 (0.22, 1.03)

*P<0.05; **P<0.01; ***P<0.001;

Table 4-6. Crude estimates of associations between baseline HRQOL variables and primary treatment (odds ratios and 95% confidence intervals)

		RP vs. RT	RP vs. EM	RP vs. HT
KPS	High vs. low (ref)	1.59 (1.05, 2.38)*	1.05 (0.76, 1.45)	2.00 (1.27, 3.13)**
SF-36				
PF	High vs. low (ref)	2.78 (2.13, 3.70)***	3.85 (2.78, 5.56)***	5.26 (3.57, 7.69)***
RO	High vs. low (ref)	2.00 (1.56, 2.50)***	3.23 (2.38, 4.35)***	3.13 (2.17, 4.55)***
BP	High vs. low (ref)	1.52 (1.19, 1.92)**	2.04 (1.49, 2.78)***	2.22 (1.54, 3.23)***
GH	High vs. low (ref)	2.00 (1.56, 2.56)***	2.78 (2.04, 3.85)***	3.45 (2.38, 5.00)***
RE	High vs. low (ref)	1.52 (1.16, 1.92)**	2.00 (1.45, 2.78)***	1.89 (1.30, 2.78)**
VT	High vs. low (ref)	2.00 (1.56, 2.50)***	2.63 (1.92, 3.57)***	3.33 (2.33, 4.76)***
SO	High vs. low (ref)	1.37 (1.10, 1.69)**	1.64 (1.22, 2.22)**	1.89 (1.35, 2.70)***
MH	High vs. low (ref)	1.32 (1.06, 1.61)*	1.23 (0.93, 1.64)	1.39 (0.99, 1.96)
UCLA-PCI				
UF	High vs. low (ref)	1.23 (0.99, 1.52)	1.27 (0.94, 1.69)	1.49 (1.06, 2.08)*
UB	High vs. low (ref)	1.14 (0.93, 1.41)	1.43 (1.06, 1.89)*	1.56 (1.11, 2.17)*
BF	High vs. low (ref)	1.30 (1.06, 1.61)*	1.39 (1.03, 1.85)*	1.89 (1.35, 2.63)***
BB	High vs. low (ref)	1.49 (1.19, 1.89)**	1.85 (1.35, 2.50)***	2.22 (1.56, 3.13)***
SF	High vs. low (ref)	1.96 (1.59, 2.44)***	1.96 (1.45, 2.63)***	3.57 (2.50, 5.26)***
SB	High vs. low (ref)	1.39 (1.12, 1.72)**	1.82 (1.35, 2.44)***	1.61 (1.12, 2.27)**

*P<0.05; **P<0.01; ***P<0.001;

Table 4-6. Continued

		RT Vs. EM	RT vs. HT	EM vs. HT
KPS	High vs. low (ref)	0.67 (0.39, 1.15)	1.27 (0.74, 2.17)	1.89 (1.11, 3.23)*
SF-36				
PF	High vs. low (ref)	1.39 (1.02, 1.85)*	1.89 (1.35, 2.63)***	1.37 (0.93, 2.04)
RO	High vs. low (ref)	1.61 (1.22, 2.17)**	1.56 (1.12, 2.22)**	0.97 (0.65, 1.43)
BP	High vs. low (ref)	1.33 (0.99, 1.79)	1.47 (1.03, 2.08)*	1.09 (0.73, 1.64)
GH	High vs. low (ref)	1.41 (1.04, 1.89)*	1.72 (1.23, 2.44)**	1.22 (0.83, 1.82)
RE	High vs. low (ref)	1.33 (0.98, 1.82)	1.27 (0.88, 1.82)	0.95 (0.63, 1.45)
VT	High vs. low (ref)	1.33 (1.00, 1.79)	1.67 (1.19, 2.33)**	1.25 (0.85, 1.85)
SO	High vs. low (ref)	1.20 (0.90, 1.61)	1.39 (1.00, 1.96)*	1.15 (0.78, 1.72)
MH	High vs. low (ref)	0.94 (0.71, 1.25)	1.06 (0.76, 1.49)	1.12 (0.76, 1.67)
UCLA-PCI				
UF	High vs. low (ref)	1.03 (0.78, 1.35)	1.20 (0.87, 1.69)	1.18 (0.80, 1.75)
UB	High vs. low (ref)	1.25 (0.94, 1.64)	1.37 (0.98, 1.92)	1.10 (0.74, 1.61)
BF	High vs. low (ref)	1.06 (0.80, 1.41)	1.45 (1.04, 2.04)*	1.37 (0.93, 2.04)
BB	High vs. low (ref)	1.23 (0.93, 1.64)	1.49 (1.06, 2.08)*	1.20 (0.82, 1.79)
SF	High vs. low (ref)	0.99 (0.75, 1.32)	1.82 (1.28, 2.63)**	1.85 (1.23, 2.78)**
SB	High vs. low (ref)	1.30 (0.98, 1.72)	1.15 (0.82, 1.61)	0.88 (0.60, 1.32)

*P<0.05; **P<0.01; ***P<0.001;

Table 4-7. Estimates of associations between baseline HRQOL variables and primary treatment, adjusting for baseline sociodemographic and clinical variables (odds ratios and 95% confidence intervals)

		RP vs. RT	RP vs. EM	RP vs. HT	RT Vs. EM	RT vs. HT	EM vs. HT
KPS	High vs. low	1.60 (1.00, 2.57)*	1.03 (0.66, 1.59)	1.86 (1.16, 2.99)*	0.64 (0.35, 1.18)	1.16 (0.70, 1.92)	1.81 (1.00, 3.27)*
PF	High vs. low	1.96 (1.41, 2.71)***	2.22 (1.44, 3.42)***	2.78 (1.75, 4.41)***	1.13 (0.80, 1.61)	1.42 (0.97, 2.08)	1.25 (0.80, 1.97)
RO	High vs. low	1.36 (1.02, 1.81)*	1.94 (1.30, 2.88)**	1.66 (1.07, 2.58)*	1.43 (1.02, 1.99)*	1.22 (0.83, 1.80)	0.86 (0.55, 1.33)
GH	High vs. low	1.55 (1.15, 2.09)**	2.04 (1.36, 3.04)**	2.35 (1.50, 3.69)***	1.31 (0.94, 1.83)	1.52 (1.03, 2.23)*	1.16 (0.74, 1.80)
VT	High vs. low	1.74 (1.32, 2.28)***	2.14 (1.45, 3.17)***	2.62 (1.71, 4.02)***	1.23 (0.89, 1.71)	1.51 (1.04, 2.19)*	1.22 (0.80, 1.87)
SF	High vs. low	1.35 (1.06, 1.72)*	1.04 (0.73, 1.48)	1.77 (1.17, 2.70)**	0.77 (0.56, 1.06)	1.32 (0.89, 1.95)	1.71 (1.09, 2.67)*

*P<0.05; **P<0.01; ***P<0.001;

Table 4-8. Estimates of adjusted associations between baseline variables and primary treatment (odds ratios and 95% confidence intervals)

		RP vs. RT	RP vs. EM
Age	65-67 (ref)	1.00	1.00
	68-70	0.69 (0.50, 0.96)*	0.45 (0.29, 0.71)***
	71-73	0.29 (0.20, 0.42)***	0.19 (0.12, 0.31)***
	74-76	0.08 (0.05, 0.12)***	0.04 (0.02, 0.07)***
	≥ 77	0.03 (0.02, 0.06)***	0.01 (0.00, 0.02)***
Race	Other race(ref)	1.00	1.00
	White	1.31 (0.80, 2.14)	1.50 (0.69, 3.28)
Marital status	Single (ref)	1.00	1.00
	Married	1.68 (1.12, 2.53)*	3.24 (1.92, 5.48)***
Income	<20K (ref)	1.00	1.00
	20K-50K	1.26 (0.86, 1.84)	1.58 (0.94, 2.64)
	>50K	1.59 (1.04, 2.43)*	1.74 (0.98, 3.08)
Insurance	Other ins (ref)	1.00	1.00
	Medicare	2.37 (1.73, 3.25)***	2.06 (1.29, 3.29)**
Diagnosis year	1995-2000 (ref)	1.00	1.00
	2001-2007	1.49 (1.14, 1.94)**	2.06 (1.42, 2.98)***
Cancer risk	Low (ref)	1.00	1.00
	Intermediate	1.43 (1.1, 1.86)**	4.87 (3.2, 7.41)***
	High	1.14 (0.75, 1.72)	3.48 (1.88, 6.45)***
Heart disease	Yes vs. no (ref)	0.49 (0.36, 0.65)***	0.47 (0.32, 0.70)***
Neurological disease/stroke	Yes vs. no (ref)	0.56 (0.33, 0.92)*	0.50 (0.27, 0.94)*
Diabetes	Yes vs. no (ref)	0.75 (0.51, 1.12)	0.45 (0.26, 0.78)**
Kidney disease	Yes vs. no (ref)	1.18 (0.69, 2.01)	0.62 (0.31, 1.25)
Lung disease	Yes vs. no (ref)	0.74 (0.48, 1.13)	0.43 (0.25, 0.74)**
Urinary condition	Yes vs. no (ref)	1.51 (1.09, 2.09)*	1.45 (0.90, 2.33)
KPS	High vs. low (ref)	1.55 (0.98, 2.46)	0.98 (0.64, 1.51)
PF	High vs. low (ref)	1.62 (1.14, 2.31)**	1.74 (1.09, 2.77)*
VT	High vs. low (ref)	1.49 (1.12, 2.00)**	1.83 (1.21, 2.77)**

Table 4-8. Continued

		RP vs. HT	RT vs. EM
Age	65-67 (ref)	1.00	1.00
	68-70	0.42 (0.20, 0.91)*	0.66 (0.41, 1.05)
	71-73	0.16 (0.07, 0.34)***	0.65 (0.40, 1.06)
	74-76	0.03 (0.02, 0.08)***	0.51 (0.32, 0.81)**
	≥ 77	0.01 (0.00, 0.01)***	0.31 (0.19, 0.48)***
Race	Other race(ref)	1.00	1.00
	White	2.66 (1.29, 5.49)**	1.14 (0.58, 2.27)
Marital status	Single (ref)	1.00	1.00
	Married	3.5 (2.02, 6.08)***	1.93 (1.28, 2.92)**
Income	<20K (ref)	1.00	1.00
	20K-50K	1.28 (0.69, 2.39)	1.25 (0.80, 1.96)
	>50K	0.98 (0.51, 1.87)	1.09 (0.65, 1.85)
Insurance	Other ins (ref)	1.00	1.00
	Medicare	2.91 (1.68, 5.03)***	0.87 (0.57, 1.32)
Diagnosis year	1995-2000 (ref)	1.00	1.00
	2001-2007	1.55 (1.02, 2.37)*	1.39 (1.01, 1.91)*
Cancer risk	Low (ref)	1.00	1.00
	Intermediate	1.37 (0.86, 2.19)	3.42 (2.35, 4.96)***
	High	0.58 (0.32, 1.05)	3.05 (1.81, 5.16)***
Heart disease	Yes vs. no (ref)	0.46 (0.30, 0.71)***	0.96 (0.69, 1.33)
Neurological disease/stroke	Yes vs. no (ref)	0.41 (0.21, 0.82)*	0.90 (0.55, 1.48)
Diabetes	Yes vs. no (ref)	0.38 (0.22, 0.66)***	0.59 (0.37, 0.95)*
Kidney disease	Yes vs. no (ref)	2.93 (0.96, 8.91)	0.53 (0.30, 0.95)*
Lung disease	Yes vs. no (ref)	1.04 (0.52, 2.10)	0.58 (0.37, 0.92)*
Urinary condition	Yes vs. no (ref)	0.99 (0.61, 1.60)	0.96 (0.64, 1.43)
KPS	High vs. low (ref)	1.75 (1.10, 2.78)*	0.63 (0.35, 1.15)
PF	High vs. low (ref)	2.03 (1.24, 3.33)**	1.07 (0.74, 1.55)
VT	High vs. low (ref)	2.07 (1.30, 3.27)**	1.23 (0.87, 1.74)

Table 4-8. Continued

		RT vs. HT	EM vs. HT
Age	65-67 (ref)	1.00	1.00
	68-70	0.61 (0.28, 1.32)	0.93 (0.41, 2.12)
	71-73	0.53 (0.24, 1.16)	0.81 (0.35, 1.87)
	74-76	0.46 (0.22, 0.97)*	0.89 (0.40, 1.98)
	≥ 77	0.17 (0.08, 0.35)***	0.57 (0.27, 1.20)
Race	Other race(ref)	1.00	1.00
	White	2.03 (1.08, 3.83)*	1.77 (0.80, 3.94)
Marital status	Single (ref)	1.00	1.00
	Married	2.08 (1.32, 3.29)**	1.08 (0.65, 1.80)
Income	<20K (ref)	1.00	1.00
	20K-50K	1.02 (0.57, 1.81)	0.81 (0.46, 1.45)
	>50K	0.62 (0.33, 1.15)	0.56 (0.30, 1.06)
Insurance	Other ins (ref)	1.00	1.00
	Medicare	1.23 (0.74, 2.04)	1.41 (0.76, 2.62)
Diagnosis year	1995-2000 (ref)	1.00	1.00
	2001-2007	1.04 (0.72, 1.52)	0.75 (0.49, 1.16)
Cancer risk	Low (ref)	1.00	1.00
	Intermediate	0.96 (0.63, 1.48)	0.28 (0.17, 0.48)***
	High	0.51 (0.31, 0.85)**	0.17 (0.09, 0.32)***
Heart disease	Yes vs. No. (ref)	0.94 (0.65, 1.37)	0.98 (0.64, 1.51)
Neurological disease/stroke	Yes vs. No. (ref)	0.74 (0.43, 1.28)	0.82 (0.44, 1.55)
Diabetes	Yes vs. No. (ref)	0.51 (0.32, 0.81)**	0.86 (0.48, 1.53)
Kidney disease	Yes vs. No. (ref)	2.49 (0.87, 7.11)	4.69 (1.56, 14.12)**
Lung disease	Yes vs. No. (ref)	1.42 (0.76, 2.64)	2.45 (1.24, 4.83)*
Urinary condition	Yes vs. No. (ref)	0.66 (0.43, 1.00)*	0.69 (0.42, 1.12)
KPS	High vs. low(ref)	1.13 (0.69, 1.85)	1.78 (1.00, 3.19)
PF	High vs. low (ref)	1.25 (0.83, 1.89)	1.17 (0.72, 1.90)
VT	High vs. low (ref)	1.38 (0.93, 2.06)	1.13 (0.72, 1.78)

*P<0.05; **P<0.01; ***P<0.001;

Table 4-9. Baseline sociodemographic variable distributions in CaPSURE elderly men with low- or intermediate-risk prostate cancer: DT vs. CT

		Overall, n (%) (N=1,700)		DT, n (%) (N=1,338)		CT, n (%) (N=362)		Odds ratio†
Age	65-67 (ref)	410	(24.1)	377	(28.2)	33	(9.1)	1.00
	68-70	432	(25.4)	383	(28.6)	49	(13.5)	0.68
	71-73	287	(16.9)	233	(17.4)	54	(14.9)	0.38***
	74-76	275	(16.2)	198	(14.8)	77	(21.3)	0.23***
	>=77	296	(17.4)	147	(11.0)	149	(41.2)	0.09***
Race	Other (ref)	1,548	(91.1)	1,232	(92.1)	316	(87.3)	1.28
	White	114	(6.7)	86	(6.4)	28	(7.7)	1.37
	Missing	38	(2.2)	20	(1.5)	18	(5.0)	--
Marital status	Single(ref)	1,425	(83.8)	1,160	(86.7)	265	(73.2)	1.00
	Married	230	(13.5)	153	(11.4)	77	(21.3)	2.20***
	Missing	45	(2.6)	25	(1.9)	20	(5.5)	--
Education	<HS (ref)	267	(15.7)	193	(14.4)	74	(20.4)	1.00
	HS / SC	770	(45.3)	598	(44.7)	172	(47.5)	1.34
	≥College	617	(36.3)	518	(38.7)	99	(27.3)	1.95***
	Missing	46	(2.7)	29	(2.2)	17	(4.7)	--
Annual house hold Income	<20K (ref)	234	(13.8)	168	(12.6)	66	(18.2)	1.00
	20K-50K	729	(42.9)	585	(43.7)	144	(39.8)	1.70*
	>50K	520	(30.6)	437	(32.7)	83	(22.9)	2.08***
	Missing	217	(12.8)	148	(11.1)	69	(19.1)	--
Insurance	Other (ref)	1,320	(77.6)	1,048	(78.3)	272	(75.1)	1.00
	Medicare	322	(18.9)	252	(18.8)	70	(19.3)	1.10
	Missing	58	(3.4)	38	(2.8)	20	(5.5)	--
Smoking status	Not current (ref)	101	(5.9)	82	(6.1)	19	(5.2)	1.00
	Current	1,548	(91.1)	1,225	(91.6)	323	(89.2)	1.11
	Missing	51	(3.0)	31	(2.3)	20	(5.5)	--
Diagnosis year	1995-2000 (ref)	511	(30.1)	392	(29.3)	119	(32.9)	1.00
	2001-2007	1,189	(69.9)	946	(70.7)	243	(67.1)	1.18

†All odds ratio were calculated after the missing imputation.

Table 4-10. Baseline clinical variable distributions in CaPSURE elderly men with low- or intermediate-risk prostate cancer: DT vs. CT

		Overall, n (%) (N=1,700)		DT, n (%) (N=1,338)		CT, n (%) (N=362)		Odds ratio[†]
Tumor stage	T1a-T2a (ref)	1,344	(79.1)	1,044	(78.0)	300	(82.9)	1.00
	T2b-T2c	356	(20.9)	294	(22.0)	62	(17.1)	1.36
Tumor grade	2-4 (ref)	42	(2.5)	21	(1.6)	21	(5.8)	1.00
	5-6	1,137	(66.9)	885	(66.1)	252	(69.6)	3.51
	7	521	(30.6)	432	(32.3)	89	(24.6)	4.85***
PSA	<10ng/mL(ref)	1296	(76.2)	1,043	(78.0)	253	(69.9)	1.00
	10-20 ng/mL	276	(16.2)	210	(15.7)	66	(18.2)	0.78
	>20 ng/mL	67	(3.9)	44	(3.3)	23	(6.4)	0.45*
	Missing	61	(3.6)	41	(3.1)	20	(5.5)	--
BMI	<25 (ref)	484	(28.5)	364	(27.2)	120	(33.1)	1.00
	25-29.9	825	(48.5)	673	(50.3)	152	(42.0)	1.49*
	>=30	326	(19.2)	261	(19.5)	65	(18.0)	1.35
	Missing	65	(3.8)	40	(3.0)	25	(6.9)	--
Comorbidity	0 (ref)	155	(9.1)	129	(9.6)	26	(7.2)	1.00
	1	410	(24.1)	344	(25.7)	66	(18.2)	1.03
	2	469	(27.6)	388	(29.0)	81	(22.4)	0.92
	3 or more	624	(36.7)	455	(34.0)	169	(46.7)	0.55*
	Missing	42	(2.5)	22	(1.6)	20	(5.5)	--
Heart disease	No (ref)	462	(27.2)	335	(25.0)	127	(35.1)	1.00
	Yes	1,196	(70.4)	981	(73.3)	215	(59.4)	0.59***
	Missing	42	(2.5)	22	(1.6)	20	(5.5)	--
Neurological disease/stroke	No (ref)	145	(8.5)	99	(7.4)	46	(12.7)	1.00
	Yes	1,513	(89.0)	1,217	(91.0)	296	(81.8)	0.54*
	Missing	42	(2.5)	22	(1.6)	20	(5.5)	--
Other cancer	No (ref)	278	(16.4)	218	(16.3)	60	(16.6)	1.00
	Yes	1,380	(81.2)	1,098	(82.1)	282	(77.9)	0.94
	Missing	42	(2.5)	22	(1.6)	20	(5.5)	--

[†]All odds ratio were calculated after the missing imputation.

Table 4-10.Continued

		Overall, n (%) (N=1,700)		DT, n (%) (N=1,338)		CT, n (%) (N=362)		Odds ratio[†]
Diabetes	No (ref)	208	(12.2)	145	(10.8)	63	(17.4)	1.00
	Yes	1,450	(85.3)	1,171	(87.5)	279	(77.1)	0.55***
	Missing	42	(2.5)	22	(1.6)	20	(5.5)	--
Kidney disease	No (ref)	93	(5.5)	68	(5.1)	25	(6.9)	1.00
	Yes	1,565	(92.1)	1,248	(93.3)	317	(87.6)	0.67
	Missing	42	(2.5)	22	(1.6)	20	(5.5)	--
Hypertension	No (ref)	837	(49.2)	653	(48.8)	184	(50.8)	1.00
	Yes	821	(48.3)	663	(49.6)	158	(43.6)	0.86
	Missing	42	(2.5)	22	(1.6)	20	(5.5)	--
Arthritis	No (ref)	771	(45.4)	606	(45.3)	165	(45.6)	1.00
	Yes	887	(52.2)	710	(53.1)	177	(48.9)	0.93
	Missing	42	(2.5)	22	(1.6)	20	(5.5)	--
Blood disease	No (ref)	44	(2.6)	35	(2.6)	9	(2.5)	1.00
	Yes	1,614	(94.9)	1,281	(95.7)	333	(92.0)	0.97
	Missing	42	(2.5)	22	(1.6)	20	(5.5)	--
GI disease	No (ref)	261	(15.4)	204	(15.2)	57	(15.7)	1.00
	Yes	1,397	(82.2)	1,112	(83.1)	285	(78.7)	0.95
	Missing	42	(2.5)	22	(1.6)	20	(5.5)	--
Lung disease	No (ref)	159	(9.4)	118	(8.8)	41	(11.3)	1.00
	Yes	1,499	(88.2)	1,198	(89.5)	301	(83.1)	0.70
	Missing	42	(2.5)	22	(1.6)	20	(5.5)	--
Urinary condition	No (ref)	306	(18.0)	228	(17.0)	78	(21.5)	1.00
	Yes	1,352	(79.5)	1,088	(81.3)	264	(72.9)	0.74*
	Missing	42	(2.5)	22	(1.6)	20	(5.5)	--
Other disease	0 (ref)	126	(7.4)	105	(7.8)	21	(5.8)	1.00
	≥ 1	1,532	(90.1)	1,211	(90.5)	321	(88.7)	1.37
	Missing	42	(2.5)	22	(1.6)	20	(5.5)	--

[†]All odds ratio were calculated after the missing imputation.

Table 4-11. Baseline HRQOL variable distributions in CaPSURE elderly men with low- or intermediate-risk prostate cancer: DT vs. CT

		Overall, n (%) (N=1,700)		DT, n (%) (N=1,338)		CT, n (%) (N=362)		Odds ratio[†]
KPS	Low score (ref)	470	(27.6)	354	(26.5)	116	(32.0)	1.00
	High score	101	(5.9)	68	(5.1)	33	(9.1)	0.96
	Missing	1,129	(66.4)	916	(68.5)	213	(58.8)	--
SF-36								
PF	Low score (ref)	1,276	(75.1)	1,049	(78.4)	227	(62.7)	1.00
	High score	388	(22.8)	259	(19.4)	129	(35.6)	2.26***
	Missing	36	(2.1)	30	(2.2)	6	(1.7)	--
RO	Low score (ref)	1,191	(70.1)	985	(73.6)	206	(56.9)	1.00
	High score	475	(27.9)	327	(24.4)	148	(40.9)	2.16***
	Missing	34	(2.0)	26	(1.9)	8	(2.2)	--
BP	Low score (ref)	1,215	(71.5)	988	(73.8)	227	(62.7)	1.00
	High score	453	(26.6)	327	(24.4)	126	(34.8)	1.69***
	Missing	32	(1.9)	23	(1.7)	9	(2.5)	--
GH	Low score (ref)	1,211	(71.2)	994	(74.3)	217	(59.9)	1.00
	High score	453	(26.6)	318	(23.8)	135	(37.3)	1.92***
	Missing	36	(2.1)	26	(1.9)	10	(2.8)	--
RE	Low score (ref)	1,293	(76.1)	1,041	(77.8)	252	(69.6)	1.00
	High score	372	(21.9)	272	(20.3)	100	(27.6)	1.52*
	Missing	35	(2.1)	25	(1.9)	10	(2.8)	--
VT	Low score (ref)	1,147	(67.5)	943	(70.5)	204	(56.4)	1.00
	High score	530	(31.2)	378	(28.3)	152	(42.0)	1.84***
	Missing	23	(1.4)	17	(1.3)	6	(1.7)	--
SO	Low score (ref)	1,085	(63.8)	877	(65.5)	208	(57.5)	1.00
	High score	576	(33.9)	430	(32.1)	146	(40.3)	1.43*
	Missing	39	(2.3)	31	(2.3)	8	(2.2)	--
MH	Low score (ref)	961	(56.5)	761	(56.9)	200	(55.2)	1.00
	High score	713	(41.9)	558	(41.7)	155	(42.8)	1.07
	Missing	26	(1.5)	19	(1.4)	7	(1.9)	--
UCLA-PCI								
UF	Low score (ref)	996	(58.6)	794	(59.3)	202	(55.8)	1.00
	High score	673	(39.6)	518	(38.7)	155	(42.8)	1.18
	Missing	31	(1.8)	26	(1.9)	5	(1.4)	--
UB	Low score (ref)	964	(56.7)	778	(58.1)	186	(51.4)	1.00
	High score	701	(41.2)	534	(39.9)	167	(46.1)	1.32*
	Missing	35	(2.1)	26	(1.9)	9	(2.5)	--
BF	Low score (ref)	968	(56.9)	779	(58.2)	189	(52.2)	1.00
	High score	721	(42.4)	553	(41.3)	168	(46.4)	1.25
	Missing	11	(0.6)	6	(0.4)	5	(1.4)	--
BB	Low score (ref)	1,147	(67.5)	928	(69.4)	219	(60.5)	1.00
	High score	533	(31.4)	393	(29.4)	140	(38.7)	1.49*
	Missing	20	(1.2)	17	(1.3)	3	(0.8)	--
SF	Low score (ref)	788	(46.4)	655	(49.0)	133	(36.7)	1.00
	High score	859	(50.5)	643	(48.1)	216	(59.7)	1.63***
	Missing	53	(3.1)	40	(3.0)	13	(3.6)	--
SB	Low score (ref)	984	(57.9)	805	(60.2)	179	(49.4)	1.00
	High score	612	(36.0)	462	(34.5)	150	(41.4)	1.52*
	Missing	104	(6.1)	71	(5.3)	33	(9.1)	--

[†]All odds ratio were calculated after the missing imputation.

Table 4-12. Crude associations between baseline sociodemographic variables and 10-year survival outcomes (hazard ratios and 95% confidence Intervals)

		All-cause death	Prostate cancer death	Other cause death
Age	65-67 (ref)	1.00	1.00	1.00
	68-70	1.43 (0.88, 2.31)	0.38 (0.1, 1.46)	1.8 (1.05, 3.07)*
	71-73	1.65 (0.99, 2.76)	0.6 (0.16, 2.32)	2.02 (1.14, 3.57)*
	74-76	1.86 (1.14, 3.06)*	0.93 (0.29, 2.92)	2.19 (1.25, 3.83)**
	≥ 77	3.49 (2.25, 5.42)***	1.01 (0.34, 3.03)	4.37 (2.66, 7.18)***
Race	Other races (ref)	1.00	1.00	1.00
	White	1.19 (0.63, 2.25)	0.63 (0.15, 2.71)	1.33 (0.65, 2.7)
Marital status	Single (ref)	1.00	1.00	1.00
	Married	0.78 (0.53, 1.13)	0.48 (0.18, 1.24)	0.83 (0.56, 1.25)
Education	<HS (ref)	1.00	1.00	1.00
	HS/some College	1.03 (0.72, 1.47)	0.78 (0.28, 2.22)	1.07 (0.73, 1.56)
	≥College	0.67 (0.45, 1.01)	0.68 (0.22, 2.12)	0.67 (0.44, 1.04)
Income	<20K (ref)	1.00	1.00	1.00
	20K-50K	0.77 (0.53, 1.11)	0.37 (0.12, 1.07)	0.85 (0.57, 1.27)
	>50K	0.54 (0.35, 0.84)**	0.46 (0.14, 1.52)	0.56 (0.35, 0.88)*
Insurance	Other ins (ref)	1.00	1.00	1.00
	Medicare	1.2 (0.82, 1.75)	4.5 (0.42, 48.42)	1.09 (0.75, 1.59)
Smoking status	Not current (ref)	1.00	1.00	1.00
	Current	1.92 (1.24, 2.96)**	0.04 (0, 70.63)	2.19 (1.41, 3.39)***
Diagnosis year	1995-2000 (ref)	1.00	1.00	1.00
	2001-2007	1.13 (0.85, 1.52)	0.58 (0.23, 1.44)	1.23 (0.9, 1.67)

*P<0.05; **P<0.01; ***P<0.001;

Table 4-13. Crude associations between baseline clinical variables and 10-year survival outcomes (hazard ratios and 95% confidence intervals)

		All-cause death	Prostate cancer death	Other cause death
Tumor stage	T1-T2a (ref)	1.00	1.00	1.00
	T2b-T2c	1.33 (0.99, 1.79)	1.79 (0.78, 4.11)	1.28 (0.93, 1.75)
Tumor grade	2-4 (ref)	1.00	1.00	1.00
	5-6	1.08 (0.76, 1.55)	3.19 (1.29, 7.88)*	0.91 (0.62, 1.35)
	7	1.62 (1.00, 2.62)	3.28 (0.91, 11.89)	1.48 (0.88, 2.50)
PSA level	<10 (ref)	1.00	1.00	1.00
	10-20	1.46 (0.60, 3.58)	9.51E6.00 (0, +∞)	1.34 (0.55, 3.28)
	>20	1.86 (0.75, 4.59)	2.94E6.00 (0, +∞)	1.50 (0.60, 3.74)
BMI	<25 (ref)	1.00	1.00	1.00
	25-29.9	0.91 (0.67, 1.24)	0.91 (0.38, 2.18)	0.91 (0.66, 1.26)
	>=30	0.86 (0.57, 1.28)	0.64 (0.17, 2.38)	0.88 (0.58, 1.36)
Heart disease	Yes vs. No (ref)	1.33 (1.00, 1.77)*	0.99 (0.41, 2.38)	1.38 (1.02, 1.86)*
Neurological disease/stroke	Yes vs. No (ref)	1.95 (1.35, 2.81)***	2.04 (0.69, 5.98)	1.94 (1.32, 2.86)***
Other cancer	Yes vs. No (ref)	1.06 (0.74, 1.52)	2.17 (0.9, 5.26)	0.95 (0.64, 1.41)
Diabetes	Yes vs. No (ref)	1.67 (1.17, 2.40)**	1.14 (0.34, 3.83)	1.75 (1.20, 2.54)**
Kidney disease	Yes vs. No (ref)	0.77 (0.39, 1.51)	1.5 (0.35, 6.39)	0.68 (0.32, 1.46)
Hypertension	Yes vs. No (ref)	1.21 (0.93, 1.59)	0.57 (0.24, 1.33)	1.33 (1.00, 1.77)
Arthritis	Yes vs. No (ref)	0.94 (0.72, 1.24)	1.62 (0.72, 3.65)	0.88 (0.66, 1.17)
Blood disease	Yes vs. No (ref)	1.99 (1.04, 3.84)*	0.04 (0, 4071)	2.24 (1.16, 4.32)*
GI disease	Yes vs. No (ref)	0.98 (0.69, 1.4)	0.38 (0.09, 1.64)	1.07 (0.74, 1.55)
Lung disease	Yes vs. No (ref)	1.27 (0.85, 1.91)	0.8 (0.19, 3.39)	1.34 (0.87, 2.05)
Urinary condition	Yes vs. No (ref)	1.09 (0.77, 1.54)	0.68 (0.2, 2.26)	1.15 (0.80, 1.65)
Other disease	Yes vs. No (ref)	0.98 (0.58, 1.65)	1.2 (0.28, 5.08)	0.95 (0.55, 1.67)
Number of comorbidity	0 (ref)	1.00	1.00	1.00
	1	1.09 (0.61, 1.95)	0.50 (0.11, 2.24)	1.23 (0.64, 2.34)
	2	1.29 (0.73, 2.28)	1.00 (0.27, 3.69)	1.36 (0.72, 2.57)
	3 or more	1.51 (0.86, 2.63)	0.69 (0.18, 2.60)	1.70 (0.91, 3.15)

*P<0.05; **P<0.01; ***P<0.001

Table 4-14. Crude associations between baseline HRQOL variables and 10-year survival outcomes (hazard ratios and 95% confidence intervals)

		All-cause death	Prostate cancer death	Other cause death
KPS	High vs. low (ref)	0.61 (0.39, 0.95)*	1.21 (0.29, 5.03)	0.55 (0.37, 0.83)**
SF-36				
PF	High vs. low (ref)	0.42 (0.32, 0.55)***	0.93 (0.37, 2.34)	0.38 (0.29, 0.51)***
RO	High vs. low (ref)	0.54 (0.41, 0.71)***	0.81 (0.35, 1.86)	0.51 (0.38, 0.68)***
BP	High vs. low (ref)	0.65 (0.49, 0.86)**	0.94 (0.38, 2.34)	0.62 (0.46, 0.83)**
GH	High vs. low (ref)	0.57 (0.43, 0.75)***	0.99 (0.41, 2.39)	0.54 (0.40, 0.71)***
RE	High vs. low (ref)	0.55 (0.42, 0.73)***	0.25 (0.11, 0.57)***	0.61 (0.46, 0.83)**
VT	High vs. low (ref)	0.54 (0.41, 0.70)***	0.84 (0.36, 1.96)	0.51 (0.38, 0.68)***
SO	High vs. low (ref)	0.72 (0.55, 0.94)*	0.77 (0.33, 1.77)	0.71 (0.53, 0.94)*
MH	High vs. low (ref)	0.66 (0.51, 0.87)**	0.86 (0.38, 1.98)	0.64 (0.48, 0.85)**
UCLA-PCI				
UF	High vs. low (ref)	0.80 (0.61, 1.05)	1.16 (0.51, 2.64)	0.77 (0.58, 1.02)
UB	High vs. low (ref)	0.76 (0.58, 1.00)*	0.73 (0.32, 1.63)	0.77 (0.58, 1.02)
BF	High vs. low (ref)	0.85 (0.65, 1.11)	1.25 (0.55, 2.87)	0.81 (0.61, 1.08)
BB	High vs. low (ref)	0.65 (0.50, 0.85)**	0.50 (0.23, 1.12)	0.67 (0.50, 0.89)**
SF	High vs. low (ref)	0.61 (0.46, 0.82)***	1.14 (0.51, 2.55)	0.56 (0.42, 0.77)***
SB	High vs. low (ref)	0.65 (0.49, 0.86)**	0.55 (0.25, 1.22)	0.66 (0.49, 0.89)**

*P<0.05; **P<0.01; ***P<0.001;

Table 4-15. Associations between baseline HRQOL variables and primary treatment, conditioning on propensity scores: DT vs. CT

Covariate		Reference propensity score (not including HRQOL)		HRQOL propensity score (including HRQOL)	
		Odds Ratio	P value	Odds Ratio	P value
KPS	High vs. low (ref)	0.86	0.37	0.98	0.89
	10 points increase	1.03	0.83	1.09	0.51
SF-36					
PF	High vs. low (ref)	1.44	0.01*	1.05	0.77
	10 points increase	1.08	0.01*	1.01	0.71
RO	High vs. low (ref)	1.53	<0.01*	1.03	0.86
	10 points increase	1.05	0.01*	1.00	1.00
BP	High vs. low (ref)	1.29	0.08	1.03	0.85
	10 points increase	1.06	0.09	1.00	0.98
GH	High vs. low (ref)	1.49	0.01*	1.05	0.73
	10 points increase	1.14	<0.01*	1.06	0.09
RE	High vs. low (ref)	1.28	0.11	1.03	0.86
	10 points increase	1.03	0.19	1.00	0.94
VT	High vs. low (ref)	1.49	0.01*	1.03	0.86
	10 points increase	1.08	0.02*	1.00	0.94
SO	High vs. low (ref)	1.20	0.18	1.00	1.00
	10 points increase	1.03	0.34	0.98	0.65
MH	High vs. low (ref)	0.94	0.69	0.99	0.95
	10 points increase	0.98	0.73	0.97	0.58
UCLA-PCI					
UF	High vs. low (ref)	0.99	0.97	1.02	0.89
	10 points increase	1.07	0.16	1.06	0.19
UB	High vs. low (ref)	1.11	0.44	1.03	0.86
	10 points increase	1.03	0.24	1.01	0.62
BF	High vs. low (ref)	1.09	0.51	1.02	0.90
	10 points increase	1.04	0.45	1.01	0.88
BB	High vs. low (ref)	1.11	0.45	1.01	0.95
	10 points increase	1.03	0.30	1.01	0.84
SF	High vs. low (ref)	1.10	0.51	1.04	0.78
	10 points increase	1.03	0.28	1.02	0.57
SB	High vs. low (ref)	1.26	0.10	1.02	0.86
	10 points increase	1.02	0.33	0.99	0.71

*P<0.05

Table 4-16. Associations between baseline HRQOL variables and primary treatment, conditioning on propensity scores: RP vs. CT

Covariate		Reference propensity score (not including HRQOL)		HRQOL propensity score (including HRQOL)	
		Odds Ratio	P value	Odds Ratio	P value
KPS	High vs. low (ref)	1.21	0.48	1.02	0.92
	10 points increase	1.68	0.04*	1.35	0.21
SF-36					
PF	High vs. low (ref)	2.49	<0.01*	1.07	0.80
	10 points increase	1.21	<0.01*	1.04	0.46
RO	High vs. low (ref)	2.05	<0.01*	1.07	0.76
	10 points increase	1.08	<0.01*	1.00	0.97
BP	High vs. low (ref)	1.65	0.02*	1.04	0.87
	10 points increase	1.09	0.07	0.98	0.71
GH	High vs. low (ref)	2.22	<0.01*	1.08	0.75
	10 points increase	1.24	<0.01*	1.06	0.30
RE	High vs. low (ref)	1.48	0.06	1.01	0.95
	10 points increase	1.06	0.06	0.99	0.86
VT	High vs. low (ref)	2.29	<0.01*	1.08	0.73
	10 points increase	1.17	<0.01*	0.99	0.87
SO	High vs. low (ref)	1.30	0.21	1.03	0.90
	10 points increase	1.05	0.37	0.96	0.51
MH	High vs. low (ref)	1.12	0.58	0.98	0.93
	10 points increase	1.06	0.38	0.99	0.85
UCLA-PCI					
UF	High vs. low (ref)	1.15	0.49	1.04	0.86
	10 points increase	1.11	0.10	1.07	0.35
UB	High vs. low (ref)	1.26	0.25	1.04	0.85
	10 points increase	1.06	0.15	1.01	0.79
BF	High vs. low (ref)	1.27	0.22	1.06	0.79
	10 points increase	1.07	0.28	0.99	0.87
BB	High vs. low (ref)	1.30	0.21	1.03	0.91
	10 points increase	1.06	0.19	1.00	0.97
SF	High vs. low (ref)	1.39	0.07	1.06	0.79
	10 points increase	1.08	0.03*	1.02	0.64
SB	High vs. low (ref)	1.46	0.07	1.05	0.83
	10 points increase	1.05	0.06	1.01	0.80

*P<0.05

Table 4-17. Associations between baseline HRQOL variables and primary treatment, conditioning on propensity scores: RT vs. CT

Covariate		Reference propensity score (not including HRQOL)		HRQOL propensity score (including HRQOL)	
		Odds Ratio	P value	Odds Ratio	P value
KPS	High vs. low (ref)	0.75	0.11	0.98	0.88
	10 points increase	0.89	0.44	1.04	0.79
SF-36					
PF	High vs. low (ref)	1.20	0.23	1.00	0.99
	10 points increase	1.04	0.14	1.01	0.87
RO	High vs. low (ref)	1.39	0.03*	1.00	1.00
	10 points increase	1.04	0.03*	1.00	0.97
BP	High vs. low (ref)	1.23	0.17	1.00	0.99
	10 points increase	1.05	0.15	1.00	0.91
GH	High vs. low (ref)	1.31	0.07	1.00	0.98
	10 points increase	1.09	0.01*	1.04	0.30
RE	High vs. low (ref)	1.22	0.21	1.01	0.96
	10 points increase	1.02	0.38	0.99	0.79
VT	High vs. low (ref)	1.33	0.05	1.00	0.97
	10 points increase	1.06	0.14	0.99	0.82
SO	High vs. low (ref)	1.15	0.34	0.99	0.94
	10 points increase	1.02	0.49	0.99	0.76
MH	High vs. low (ref)	0.90	0.48	0.99	0.94
	10 points increase	0.96	0.43	0.97	0.49
UCLA-PCI					
UF	High vs. low (ref)	0.98	0.86	1.00	1.00
	10 points increase	1.07	0.13	1.07	0.14
UB	High vs. low (ref)	1.11	0.45	1.01	0.96
	10 points increase	1.03	0.27	1.01	0.67
BF	High vs. low (ref)	1.03	0.82	1.00	1.00
	10 points increase	1.02	0.63	1.01	0.81
BB	High vs. low (ref)	1.08	0.59	1.00	1.00
	10 points increase	1.02	0.45	1.01	0.84
SF	High vs. low (ref)	1.01	0.94	1.00	0.99
	10 points increase	1.01	0.75	1.00	0.91
SB	High vs. low (ref)	1.20	0.21	1.01	0.97
	10 points increase	1.01	0.71	0.99	0.46

*P<0.05

Table 4-18. Propensity score (PS) quintile-specific hazard ratios for all-cause mortality before additional adjustment of the baseline HRQOL variables

	Quintile	PS range	Definitive treatment		Conservative treatment		Hazard ratio
			RP (n)	RT (n)	EM (n)	HT (n)	
DT vs. CT	1	0.08-0.64	13	152	117	58	0.57
	2	0.64-0.81	59	183	57	41	0.48
	3	0.81-0.89	112	176	32	20	0.22
	4	0.89-0.94	200	122	12	6	0.38
	5	0.94-0.99	227	94	10	9	0.33
RP vs. CT	1	0.003-0.17	12	--	119	64	1.17
	2	0.17-0.66	82	--	70	43	0.41
	3	0.67-0.86	156	--	21	17	0.18
	4	0.86-0.94	179	--	10	6	0.22
	5	0.94-0.99	182	--	8	4	0.49
RT vs. CT	1	0.09-0.51	--	81	96	41	0.68
	2	0.51-0.65	--	140	47	31	0.64
	3	0.65-0.75	--	150	41	27	0.20
	4	0.75-0.82	--	170	31	17	0.45
	5	0.82-0.97	--	186	13	18	0.40

Table 4-19. Propensity score (PS) quintile-specific hazard ratios for all-cause mortality after additional adjustment of the baseline HRQOL variables

	Quintile	PS range	Definitive treatment		Conservative treatment		Hazard ratio
			RP (n)	RT (n)	EM (n)	HT (n)	
DT vs. CT	1	0.05-0.64	17	142	121	60	0.61
	2	0.64-0.81	52	196	55	37	0.41
	3	0.81-0.89	127	160	32	21	0.52
	4	0.90-0.94	185	131	15	9	0.55
	5	0.94-0.99	230	98	5	7	0.16
RP vs. CT	1	0.001-0.16	14	--	118	63	1.26
	2	0.16-0.64	76	--	70	49	0.23
	3	0.65-0.87	153	--	26	15	0.43
	4-5	0.87-0.99	368	--	14	7	0.31
RT vs. CT	1	0.07-0.52	--	81	95	42	0.59
	2	0.52-0.65	--	131	54	33	0.51
	3	0.65-0.75	--	154	40	24	0.29
	4	0.75-0.83	--	170	27	21	0.59
	5	0.83-0.96	--	191	12	14	0.31

Table 4-20. Adjusted associations between primary treatment and 10-year mortality outcomes: DT vs. CT

Outcome	Method	Additional HRQOL adjustment	Hazard ratio[†]	95% CI [‡]	Relative change	Absolute change
All-cause mortality	Crude	N/A	0.35	0.16-0.77	--	--
	PS, continuous	No	0.44	0.19-1.05	3.0%	0.01
		Yes	0.46	0.19-1.08		
	PS, quintiles	No	0.43	0.21-0.91	9.3%	0.04
		Yes	0.48	0.23-1.00		
	Weighting, entire sample	No	0.43	0.19-0.96	5.7%	0.03
		Yes	0.46	0.20-1.04		
	Weighting, DT	No	0.42	0.18-0.97	6.5%	0.03
		Yes	0.44	0.19-1.05		
	Weighting, CT	No	0.50	0.24-1.05	1.9%	0.01
		Yes	0.51	0.24-1.09		
Prostate cancer-specific mortality	Crude	N/A	0.30	0.08-1.07	--	--
	PS, continuous	No	0.26	0.06-1.14	1.4%	<0.01
		Yes	0.27	0.06-1.21		
	PS, quintiles	No	0.28	0.07-1.18	0.5%	<0.01
		Yes	0.29	0.07-1.23		
	Weighting, entire sample	No	0.31	0.06-1.51	3.9%	0.01
		Yes	0.32	0.06-1.60		
	Weighting, DT	No	0.35	0.06-2.09	4.4%	0.02
		Yes	0.36	0.06-2.29		
	Weighting, CT	No	0.19	0.05-0.81	3.0%	0.01
		Yes	0.20	0.04-0.90		
Other-cause mortality	Crude	N/A	0.36	0.16-0.79	--	--
	PS, continuous	No	0.46	0.19-1.10	3.0%	0.01
		Yes	0.48	0.20-1.13		
	PS, quintiles	No	0.45	0.21-0.94	10.2%	0.05
		Yes	0.50	0.24-1.05		
	Weighting, entire sample	No	0.44	0.20-1.00	5.8%	0.03
		Yes	0.47	0.20-1.09		
	Weighting, DT	No	0.42	0.18-1.01	6.6%	0.03
		Yes	0.45	0.19-1.09		
	Weighting, CT	No	0.52	0.25-1.11	1.8%	0.01
		Yes	0.53	0.25-1.16		

[†]. All estimates were obtained as IPCW weights applied;
[‡]. All 95% CIs were based on 1000 bootstrap samples;

Table 4-21. Adjusted associations between primary treatment and 10-year mortality outcomes: RP vs. CT

Outcome	Method	Additional HRQOL adjustment	Hazard ratio[†]	95% CI [‡]	Relative change	Absolute change
All-cause mortality	Crude	N/A	0.27	0.12-0.64	--	--
	PS, continuous	No	0.37	0.11-1.21	19.9%	0.09
		Yes	0.46	0.14-1.52		
	PS, quintiles	No	0.34	0.12-0.95	18.6%	0.08
		Yes	0.42	0.15-1.15		
	Weighting, entire sample	No	0.57	0.18-1.78	29.4%	0.24
		Yes	0.81	0.23-2.81		
	Weighting, DT	No	0.36	0.11-1.16	20.3%	0.09
		Yes	0.45	0.13-1.51		
	Weighting, CT	No	0.83	0.18-3.85	19.7%	0.20
		Yes	1.03	0.21-5.19		
Prostate cancer-specific mortality	Crude	N/A	0.19	0.01-3.93	--	--
	PS, continuous	No	0.17	0.004-7.75	-22.5%	-0.03
		Yes	0.14	0.003-6.05		
	PS, quintiles	No	0.21	0.005-8.73	-28.7%	-0.05
		Yes	0.16	0.004-6.09		
	Weighting, entire sample	No	0.21	0.008-5.71	-41.1%	-0.06
		Yes	0.15	0.005-4.11		
	Weighting, DT	No	0.29	0.005-18.23	-21.3%	-0.05
		Yes	0.24	0.004-15.79		
	Weighting, CT	No	0.12	0.004-3.89	-88.1%	-0.06
		Yes	0.06	0.002-2.47		
Other-cause mortality	Crude	N/A	0.28	0.11-0.69	--	--
	PS, continuous	No	0.40	0.12-1.32	24.7%	0.13
		Yes	0.52	0.16-1.69		
	PS, quintiles	No	0.36	0.13-1.01	25.2%	0.12
		Yes	0.48	0.18-1.28		
	Weighting, entire sample	No	0.61	0.19-1.96	32.2%	0.29
		Yes	0.90	0.25-3.23		
	Weighting, DT	No	0.37	0.11-1.22	23.9%	0.12
		Yes	0.48	0.14-1.72		
	Weighting, CT	No	0.90	0.19-4.36	20.6%	0.23
		Yes	1.14	0.22-5.87		

[†]. All estimates were obtained as IPCW weights applied;
[‡]. All 95% CIs were based on 1000 bootstrap samples;

Table 4-22. Adjusted associations between primary treatment and 10-year mortality outcomes: RT vs. CT

Outcome	Method	Additional HRQOL adjustment	Hazard ratio[†]	95% CI[‡]	Relative change	Absolute change
All-cause mortality	Crude	N/A	0.43	0.20-0.95	--	--
	PS, continuous	No	0.47	0.20-1.08	1.5%	0.01
		Yes	0.47	0.20-1.12		
	PS, quintiles	No	0.46	0.22-0.98	0.6%	<0.01
		Yes	0.46	0.22-0.98		
	Weighting, entire sample	No	0.47	0.21-1.04	0.6%	<0.01
		Yes	0.47	0.21-1.06		
	Weighting, DT	No	0.46	0.19-1.12	1.6%	0.01
		Yes	0.47	0.19-1.17		
	Weighting, CT	No	0.50	0.23-1.10	-1.8%	-0.01
		Yes	0.49	0.22-1.09		
Prostate cancer-specific mortality	Crude	N/A	0.38	0.10-1.42	--	--
	PS, continuous	No	0.32	0.08-1.28	4.2%	0.01
		Yes	0.33	0.08-1.42		
	PS, quintiles	No	0.33	0.08-1.30	2.6%	0.01
		Yes	0.34	0.08-1.42		
	Weighting, entire sample	No	0.35	0.08-1.46	5.9%	0.02
		Yes	0.37	0.09-1.62		
	Weighting, DT	No	0.41	0.09-1.89	7.1%	0.03
		Yes	0.45	0.09-2.14		
	Weighting, CT	No	0.24	0.05-1.10	4.7%	0.01
		Yes	0.25	0.05-1.36		
Other-cause mortality	Crude	N/A	0.43	0.19-1.00	--	--
	PS, continuous	No	0.48	0.20-1.16	1.1%	0.01
		Yes	0.49	0.20-1.19		
	PS, quintiles	No	0.47	0.21-1.03	0.3%	<0.01
		Yes	0.47	0.21-1.03		
	Weighting, entire sample	No	0.48	0.21-1.10	0.1%	<0.01
		Yes	0.48	0.21-1.12		
	Weighting, DT	No	0.46	0.18-1.18	1.1%	0.01
		Yes	0.47	0.18-1.22		
	Weighting, CT	No	0.52	0.23-1.18	-2.2%	-0.01
		Yes	0.51	0.23-1.17		

[†]. All estimates were obtained as IPCW weights applied;
[‡]. All 95% CIs were based on 1000 bootstrap samples;

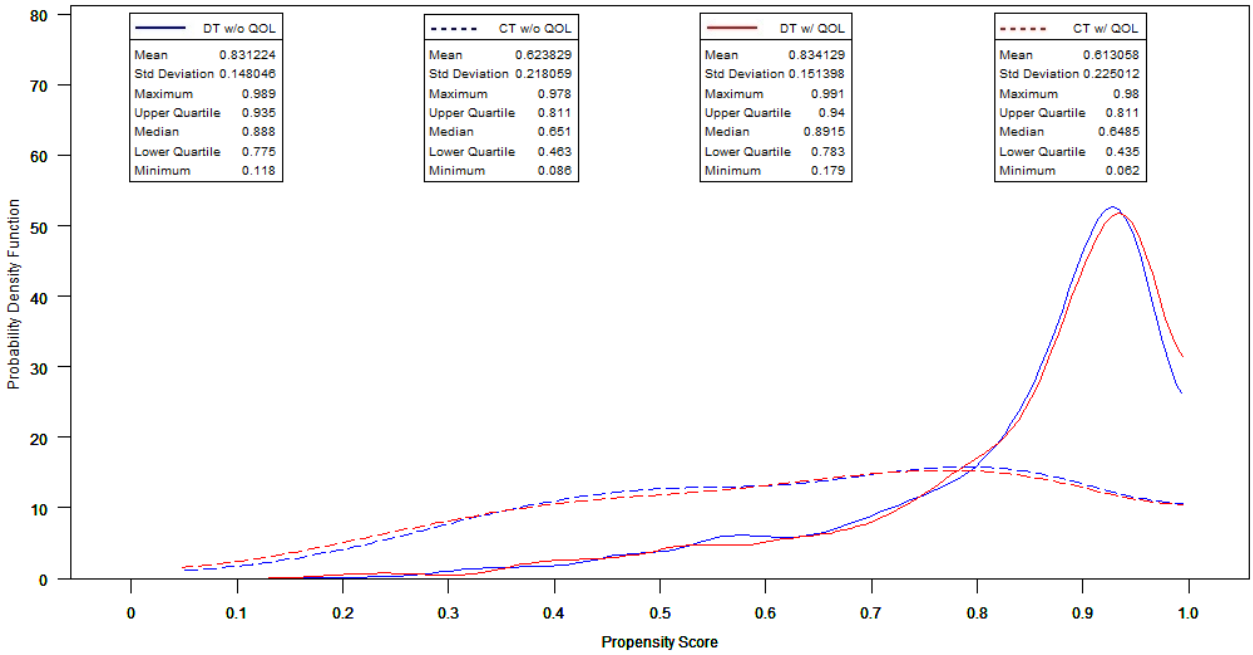


Figure 4-1. Propensity score distributions for DT vs. CT in CaPSURE elderly men (≥65 years old) with low- or intermediate-risk prostate cancer; Abbreviations: w/o QOL, without additional adjustment of baseline HRQOL variables; w/QOL, with additional adjustment of baseline HRQOL variables.

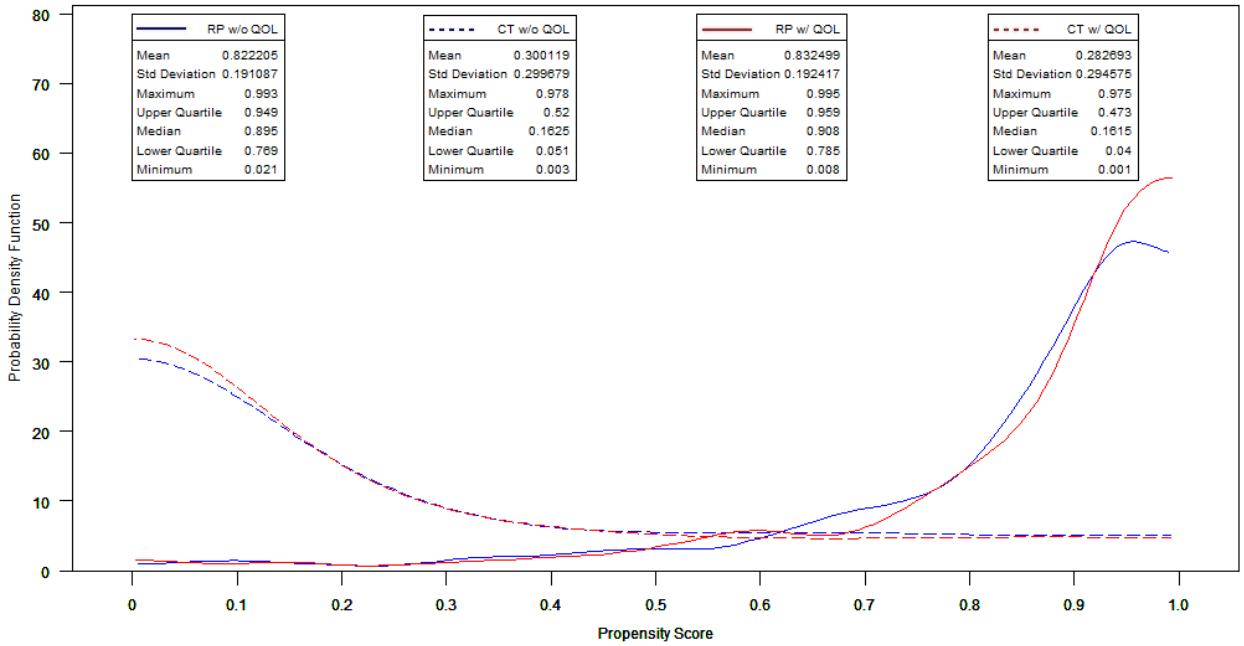


Figure 4-2. Propensity score distributions for RP vs. CT in CaPSURE elderly men (≥65 years old) with low- or intermediate-risk prostate cancer; Abbreviations: w/o QOL, without additional adjustment of baseline HRQOL variables; w/QOL, with additional adjustment of baseline HRQOL variables.

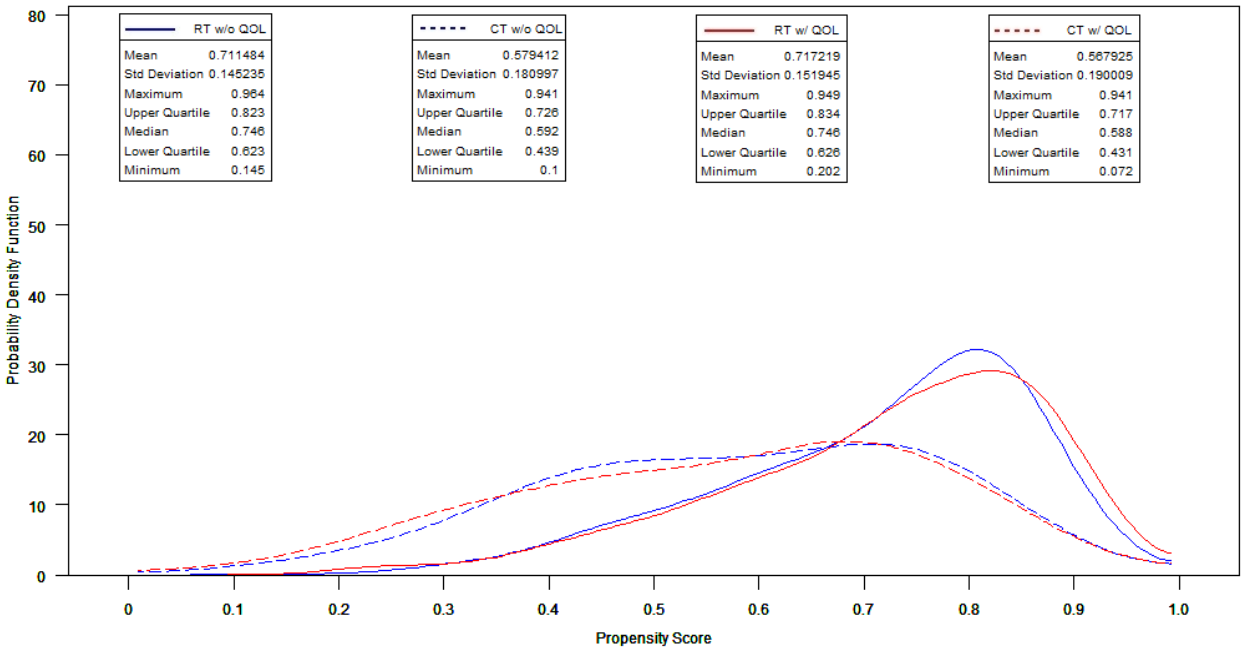
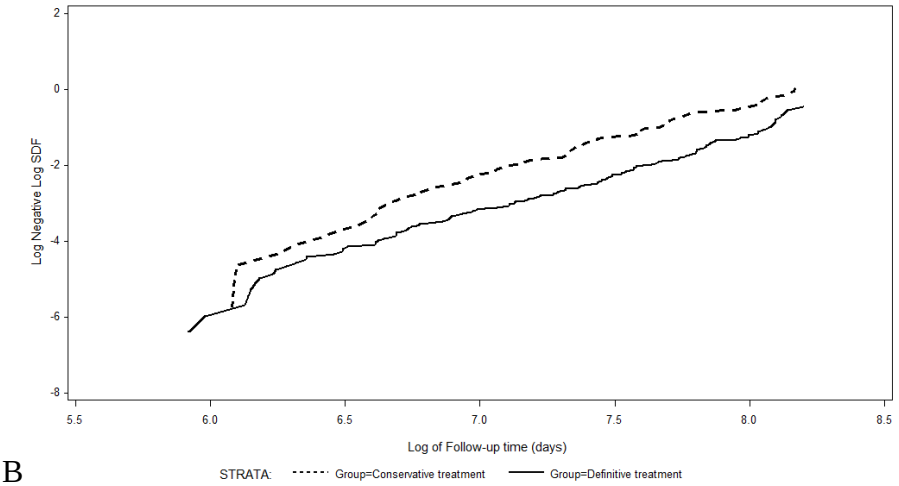
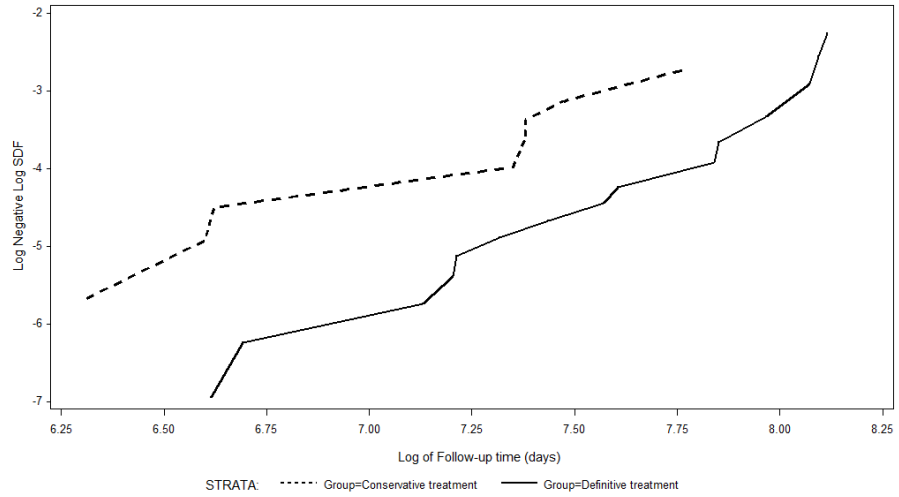


Figure 4-3. Propensity score distributionsfor RT vs. CT in CaPSURE elderly men (≥65 years old) with low- or intermediate-risk prostate cancer; Abbreviations: w/o QOL, without additional adjustment of baseline HRQOL variables; w/QOL, with additional adjustment of baseline HRQOL variables.

A



B



C

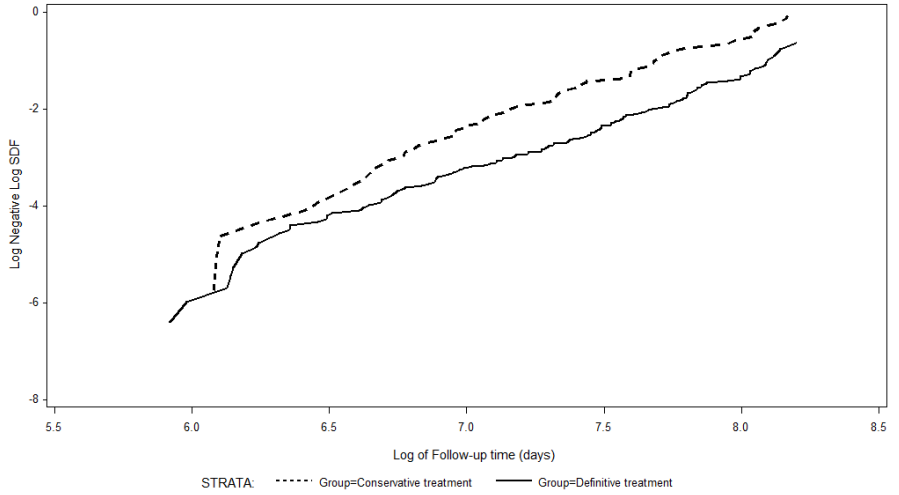
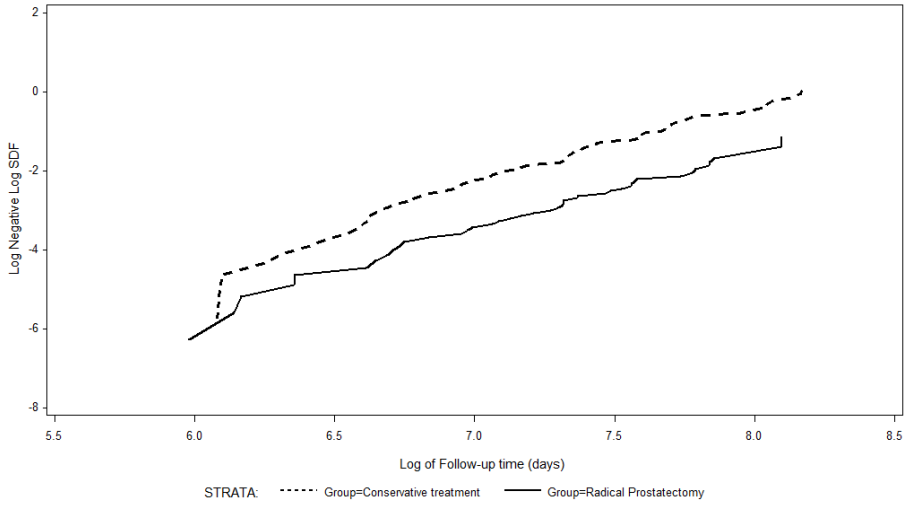
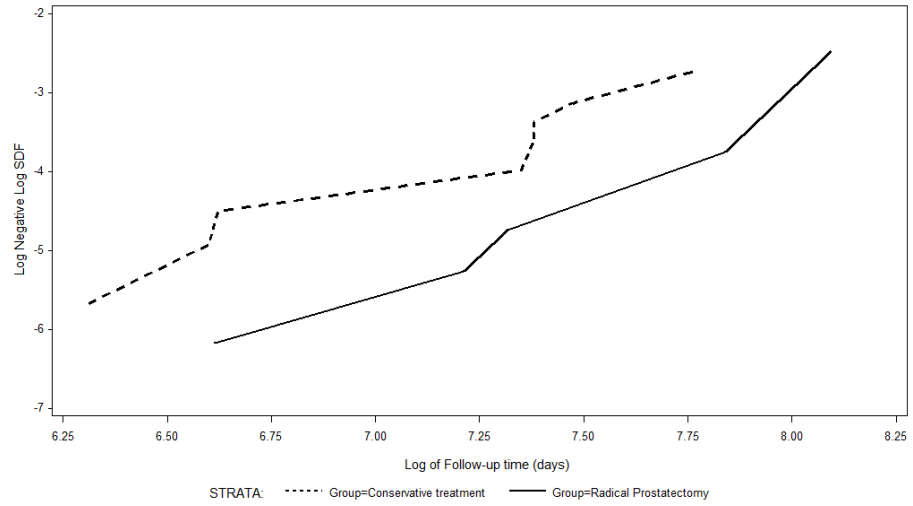


Figure 4-4. Log-log survival curves: DT vs. CT. A) all-cause mortality; B) prostate cancer-specific mortality; C) other-cause mortality.

A



B



C

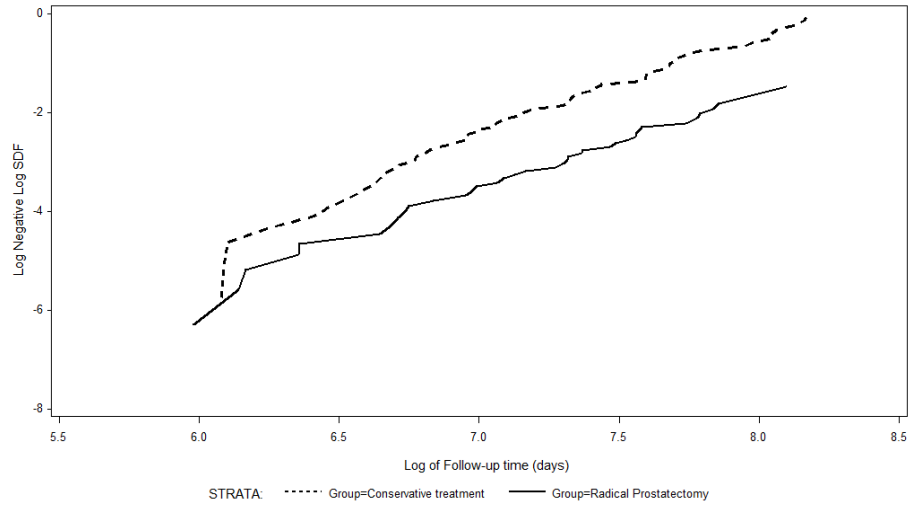
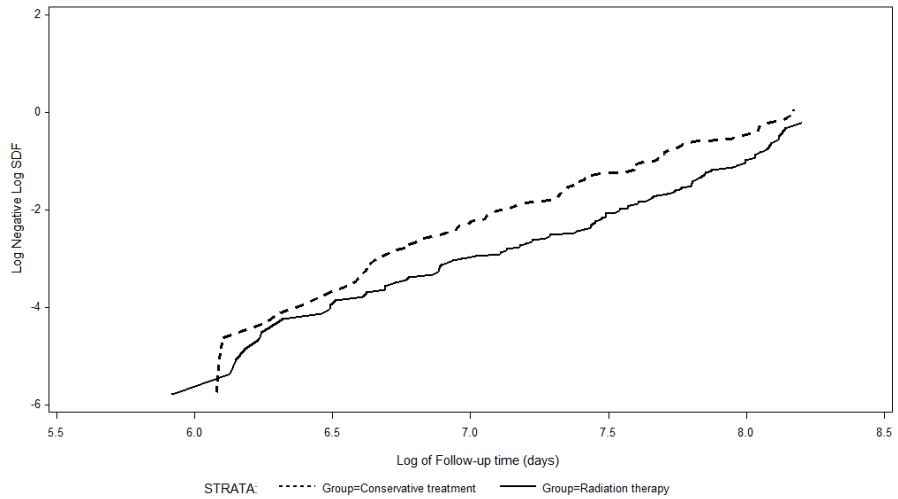
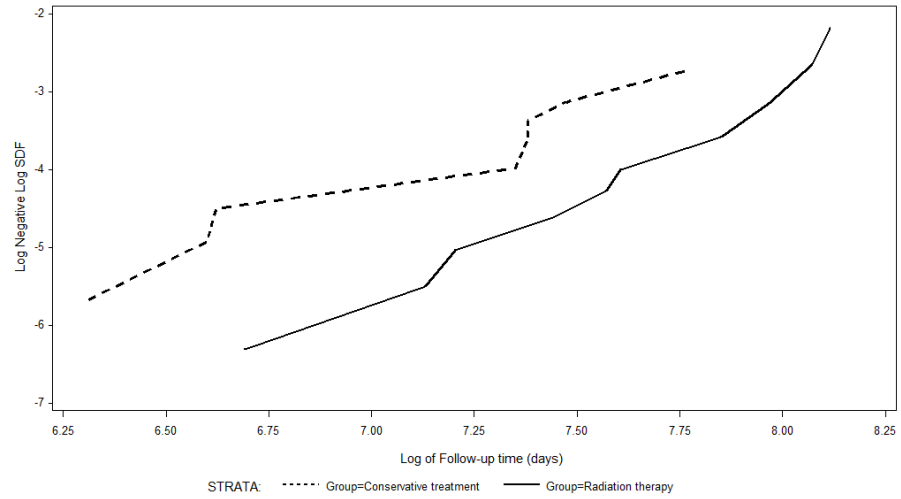


Figure 4-5. Log-log survival curves: RP vs. CT. A) all-cause mortality; B) prostate cancer-specific mortality; C) other-cause mortality.

A



B



C

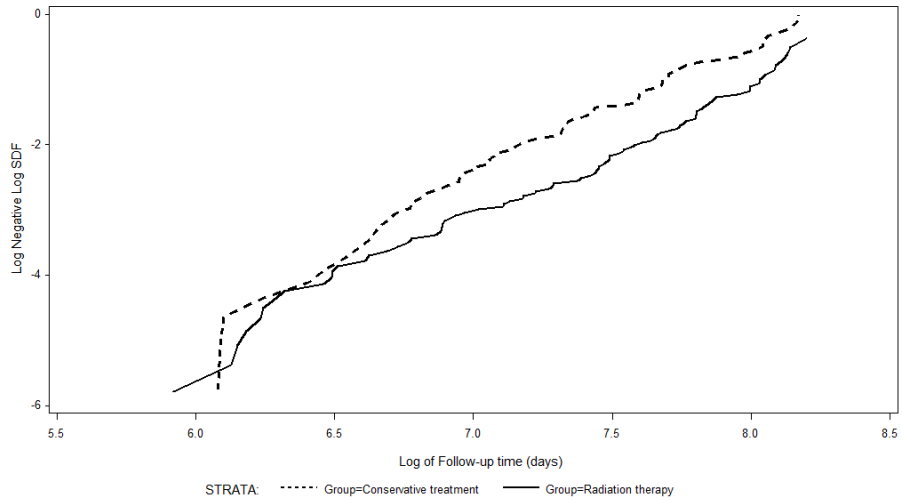


Figure 4-6. Log-log survival curves: RT vs. CT. A) all-cause mortality; B) prostate cancer-specific mortality; C) other-cause mortality.

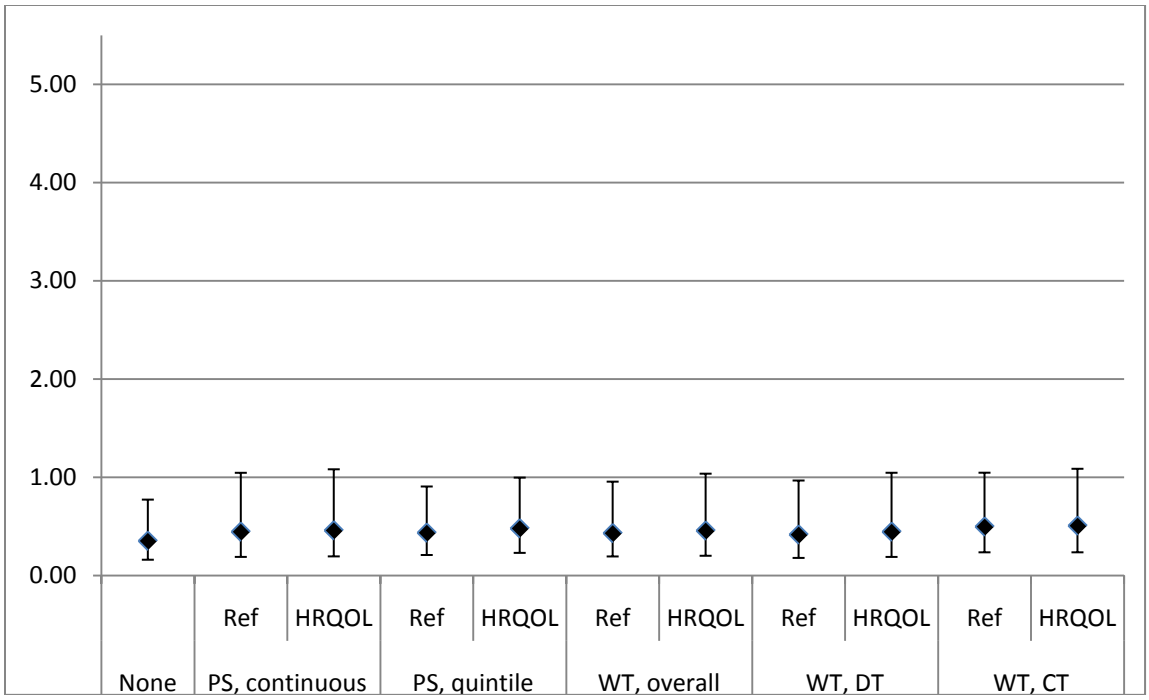


Figure 4-7. Adjusted hazard ratios by different confounding adjustment methods: DT vs. CT; Abbreviations: None, no adjustment; PS, propensity score; WT, weighting; Ref, reference model; HRQOL, HRQOL model;

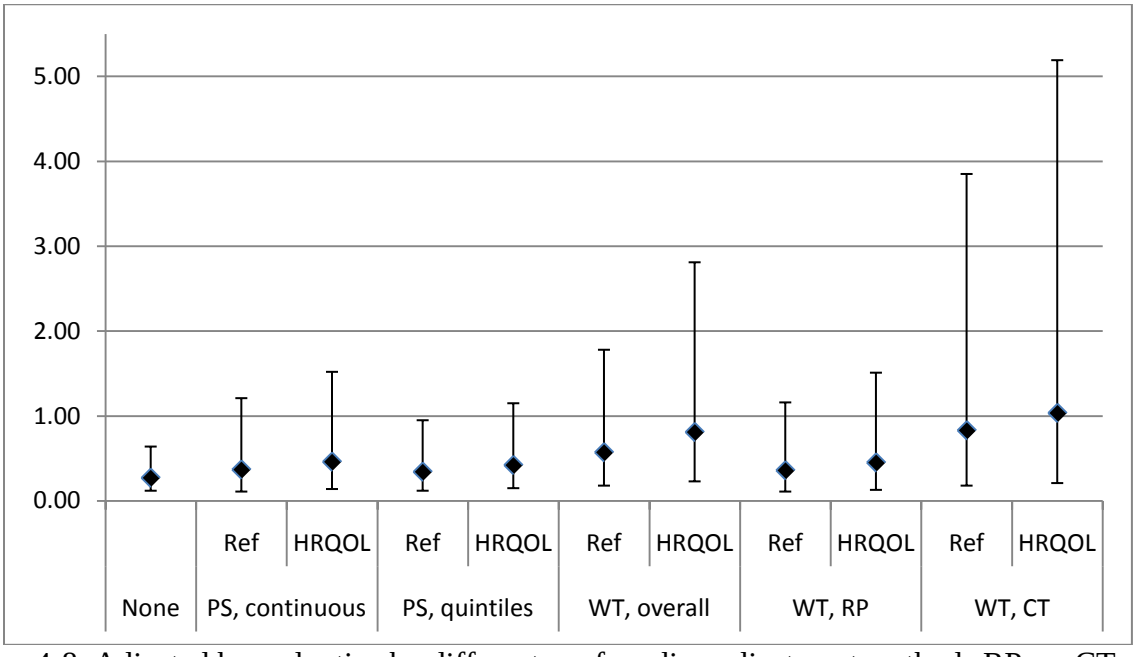


Figure 4-8. Adjusted hazard ratios by different confounding adjustment methods RP vs. CT; Abbreviations: None, no adjustment; PS, propensity score; WT, weighting; Ref, reference model; HRQOL, HRQOL model;

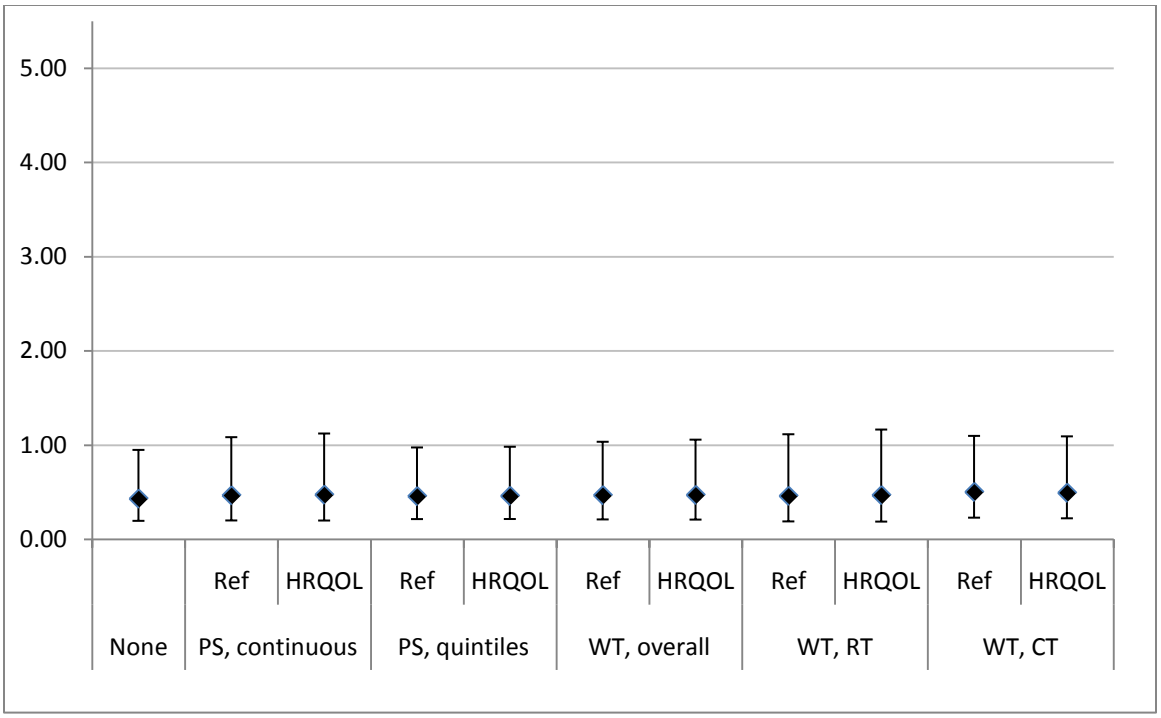


Figure 4-9. Adjusted hazard ratios by different confounding adjustment methods: RT vs. CT; Abbreviations: None, no adjustment; PS, propensity score; WT, weighting; Ref, reference model; HRQOL, HRQOL model;

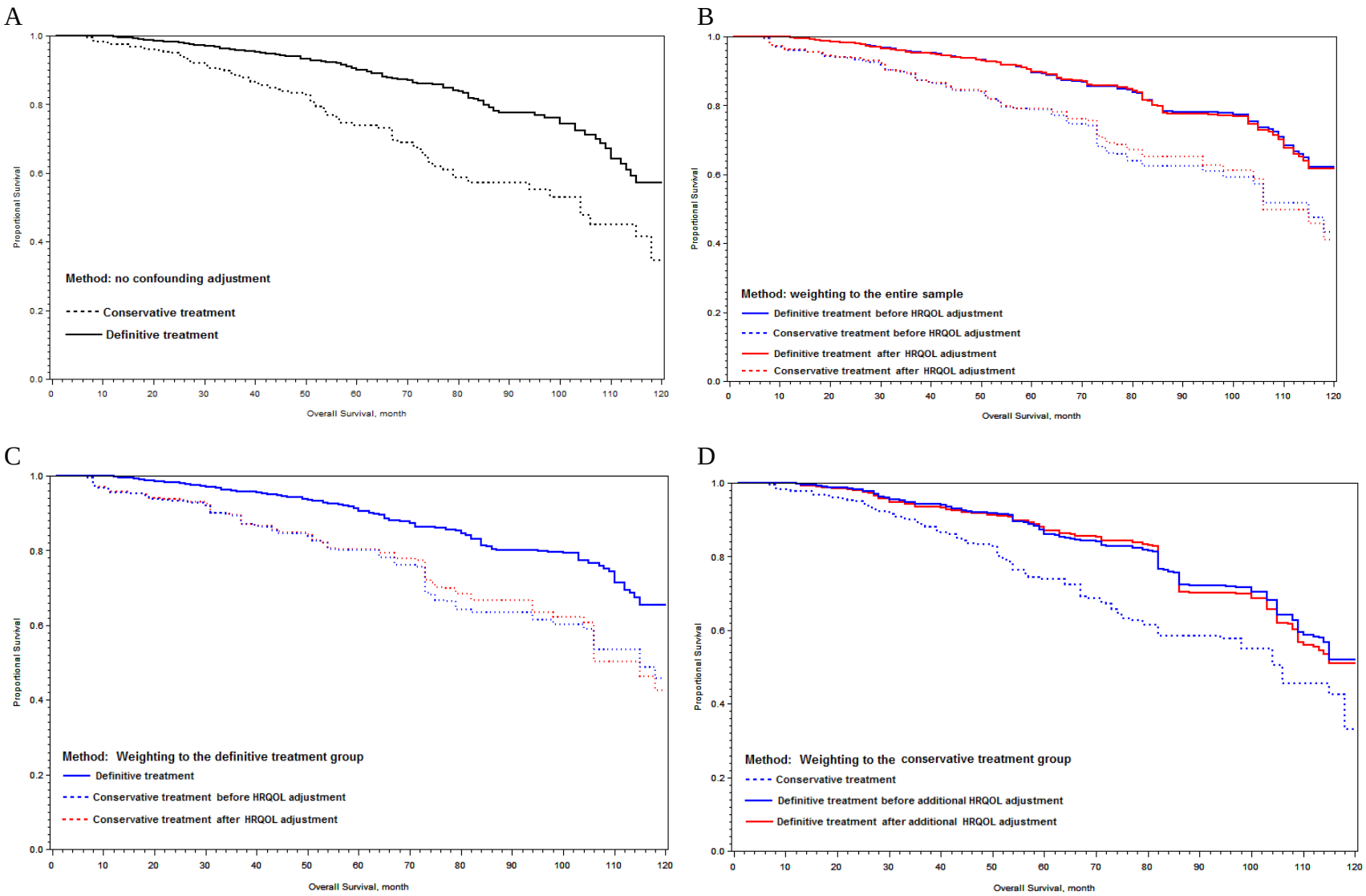


Figure 4-10. Crude and weighted survival curves: DT vs. CT. A) crude; B) weighting to the entire sample; C) weighting to the definitive treatment group; D) weighting to the conservative treatment group.

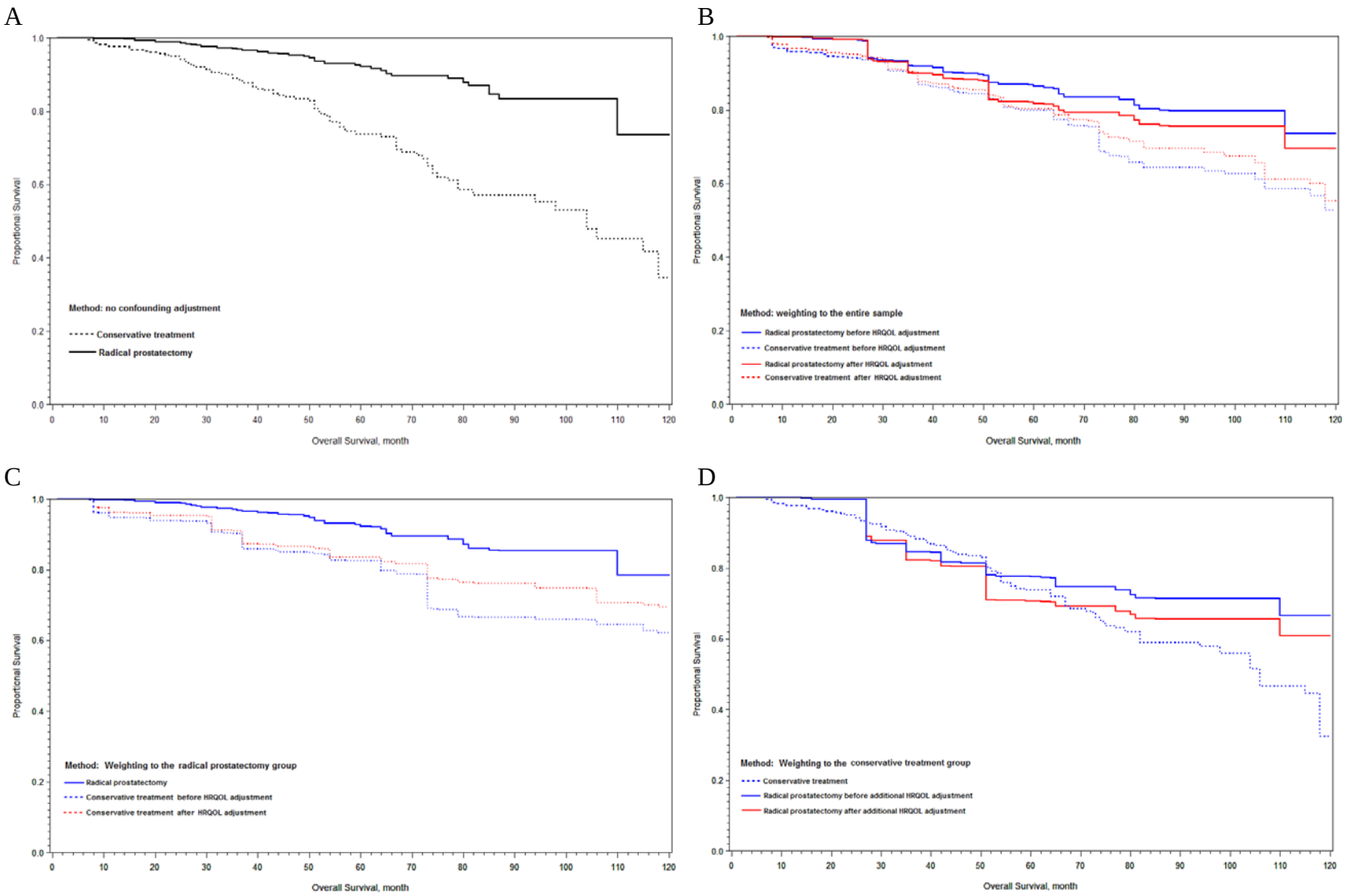


Figure 4-11. Crude and weighted survival curves: RP vs. CT. A) crude; B) weighting to the entire sample; C) weighting to the radical prostatectomy group; D) weighting to the conservative treatment group.

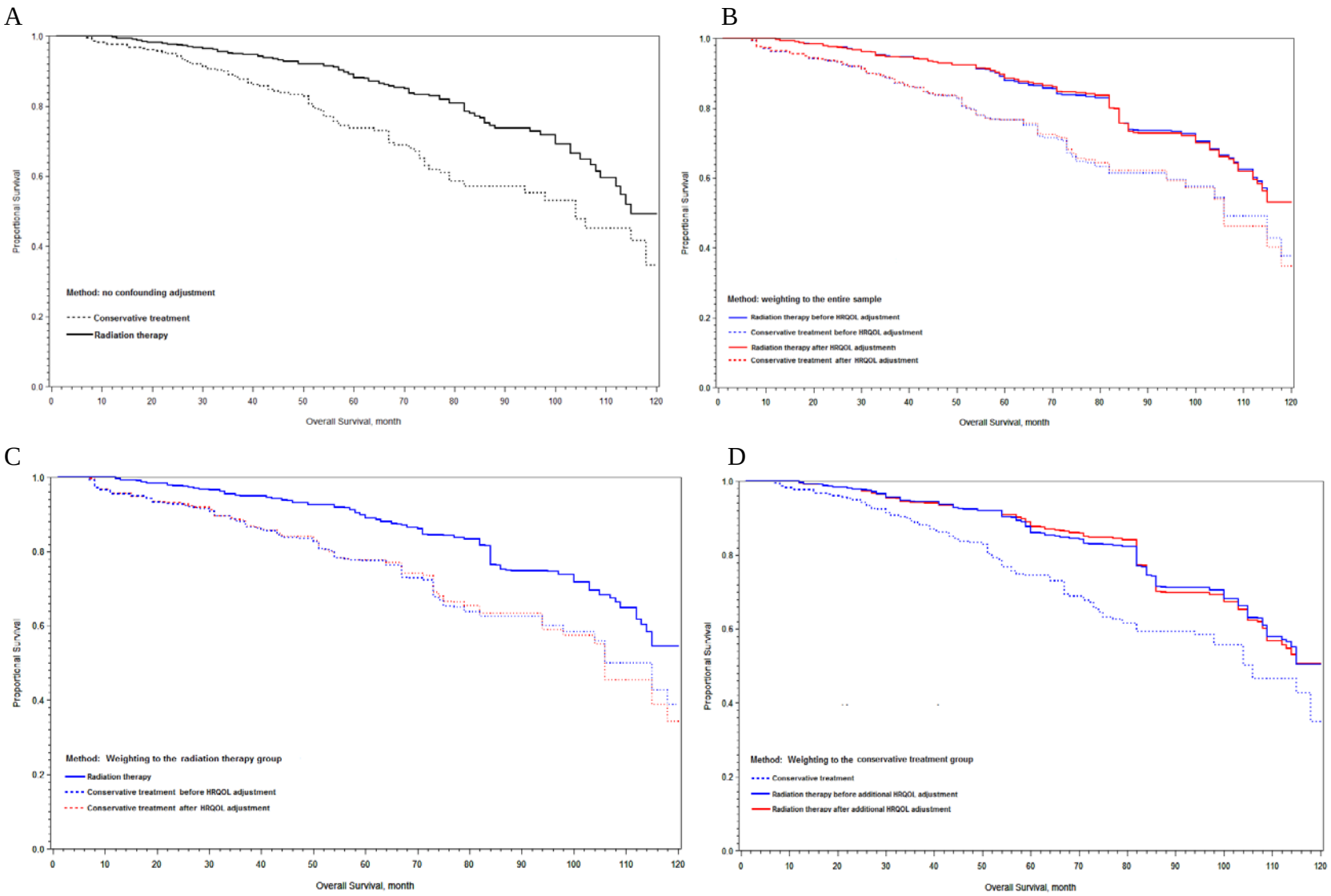


Figure 4-12. Crude and weighted survival curves: RT vs. CT. A) crude; B) weighting to the entire sample; C) weighting to the radiation therapy group; D) weighting to the conservative treatment group.

CHAPTER 5
DISCUSSION

Association between HRQOL and Primary Treatment

To our best knowledge, this is the first study that explored the associations between a comprehensive range of HRQOL variables and primary treatment for localized prostate cancer. We found that men treated with radical prostatectomy had significantly better HRQOL than the others, and men treated with radiation therapy had moderately better HRQOL than men treated conservatively. There was no significant difference between men treated with expectant management and hormonal therapy. After adjusting sociodemographic and clinical variables, six baseline HRQOL variables remained associated with primary treatment. KPS, physical functioning and vitality are the three most predictive HRQOL variables that retained in the final model.

HRQOL measures important health dimensions and strongly predicts survival. The strong associations between definitive treatment and high HRQOL scores were consistent with the current practice guidelines.[2] KPS reflects physician-assessed functional performance. It is not surprising that high KPS was associated with radical prostatectomy since physician' opinions dominate the treatment decision process.[63] Four SF-36 variables were associated with radical prostatectomy independent to sociodemographic and clinical variables. They all directly measure or highly correlate with physical health status. High physical functioning score indicates little limitation in behavioral performance of everyday physical activities. High role-physical score indicates no problem with work or other daily everyday activities as a result of physical health. High general health score reflects good self-evaluated overall health. High vitality score reflects no feeling of tiredness or worn-out.[22] Their strong associations with radical prostatectomy can be attributed to the fact that physical health status is the most prognostic factor for life expectancy

and post-surgical complication tolerance. Besides, elderly cancer patients are often screened by risk assessment tools. The most often used tools include Instrumental Activities of Daily Living, Brief Fatigue Inventory, ECOG Performance Status, and American Society for Anesthesiologist Scale.[91,92] All these instruments include items that directly assess or highly correlate with patient physical functional status. Mental health, role-emotional, and social functioning are the three SF-36 variables for mental health status. Their associations with primary treatment were insignificant after adjusting for sociodemographic and clinical factors. It appears that mental health status has minor impact on treatment decisions, or such impact can be explained by sociodemographic and clinical factors.

Out of the six PCI variables, only sexual function was associated with primary treatment adjusting for baseline sociodemographic and clinical factors. Men with good sexual function were more likely to receive radical prostatectomy than radiation therapy and hormonal therapy. There was no difference when choosing between radical prostatectomy and expectant management. This finding was consistent with previous studies. Zelidadt[10] found that prostate cancer patients with good sexual function preferred surgical treatment than non-surgical treatment. Yan[60] also found that prostate cancer patients without sexual dysfunction were more likely to receive radical prostatectomy than radiation therapy. It has been speculated that men who were not experiencing sexual dysfunction at diagnosis may discount the treatment-related side effect in the decision-making process.[10]

Despite the strong associations we found, no firm conclusion can be made regarding the exact role of HRQOL in treatment decision-making process. HRQOL often highly correlates with a wide range of socioeconomic and health factors. Many HRQOL variables are also highly

correlated with each other. The treatment decisions may be made based on one or several other unmeasured factors that highly correlate with HRQOL variables.

Another limitation of the current study is unadjusted "specialty bias". A recent study found that treatment selection was strongly associated with specialist consulted. Men solely evaluated by urologist were more likely to receive radical prostatectomy or conservative treatment than men consulted with radiation oncologist. Men consulting both radiation oncologist and urologist almost exclusively received radiation therapy.[93] Nevertheless, the observed "specialty bias" has been thought to be a consequence of urologist referral behavior. Urologists seldom refer patients to radiation oncologist unless they believe radiation therapy is more appropriate. If this is true and baseline HRQOL play a role in urologist evaluation, the "specialty bias" would have little impact on our findings.

The Confounding Effect of Baseline HRQOL

It has been hypothesized that the observed association between definitive treatment and longer survival was confounded by uncontrolled baseline HRQOL. We found nearly all the fifteen baseline HRQOL variables included in our study were strongly associated with both primary treatment and survival. Thus, they were qualified confounders according to the classic definition.

We further estimated the confounding magnitude of these baseline HRQOL variables collectively, in addition to comprehensive baseline sociodemographic and clinical factors. Significant confounding effect was observed when comparing radical prostatectomy and conservative treatment. The association between radical prostatectomy and longer all-cause survival was significantly attenuated after additional HRQOL adjustment. The hazard ratios increased approximately 18% - 29% depending on the confounding adjustment method used. It was also found that the attenuation was largely driven by attenuated association with other-cause

mortality. The plausible association with prostate cancer-specific mortality changed minimally. The observed confounding effect was minor when comparing radiation therapy vs. conservative treatment. The hazard ratios for all-cause, prostate cancer-specific and other-cause mortality remained nearly unchanged after additional HRQOL adjustment. Thus, the observed moderate confounding effect in the overall definitive treatment group lay between the significant confounding effect for radical prostatectomy and the nearly zeros confounding effect for radiation therapy. These findings were consistent with the first part of our study that radical prostatectomy was more strongly associated with high HRQOL scores than radiation therapy. Future observational studies evaluating radical prostatectomy with regard to all-cause survival should take HRQOL into consideration.

However, several red flags for substantial residual confounding were noticed even after additional adjustment of the baseline HRQOL variables. Given no unmeasured confounding, weighting to the radical prostatectomy group can be considered as a pseudo-randomized clinical trial that recruits men with health conditions permitting radical prostatectomy. We obtained a hazard ratio of 0.45 (95% CI: 0.09-2.14) by using this method, the point estimate of which conflicted with the Scandinavian trial subgroup analysis that radical prostatectomy did not benefit men older than 65 years. Moreover, men treated with radical prostatectomy or radiation therapy had nearly 50% lower risk for other-cause death, which were not plausible causal consequences of prostate cancer treatment. Considering the fact that other-cause death accounted for approximately 90% all-cause death, the observed survival benefit in the definitive treatment group was largely due to the lower other-cause mortality. These findings indicated the persistence of substantial residual confounding. Miettinen[91] pointed out that confounding may not be controllable in observational settings when treatment selection was highly influenced by

the expected outcomes. In the case of localized prostate cancer treatment, longer life expectancy greatly increased the intention to treat definitively while shorter life expectancy greatly increased the intention to treat conservatively. Life expectancy estimation is often based on a broad range of health indicators. This can be reflected by the fact that men treated definitively, particularly those treated with radical prostatectomy, had favorable characteristics for all the examined sociodemographic, clinical, and HRQOL variables. Conceivably, factors contributing to the life expectancy estimation are often too many, too complex, and too subtle to be fully captured and accurately quantified in observational studies. HRQOL assessment seems to offer additional, but still insufficient, information capture all of them. Randomized trials are needed to evaluate the true efficacy of the primary treatment effect.

Effect Modification

Besides the confounding role of baseline HRQOL, the current study compared several confounding adjustment methods. The adjusted hazard ratios varied when comparing radical prostatectomy and conservative treatment. When weighting to the radical prostatectomy group, the adjusted hazard ratio was 0.45 (95% CI: 0.13-1.51). It indicated that the observed survival in the radical prostatectomy group was longer than its counterfactual counterpart: what it would be had if these men received conservative treatment. When weighting to the conservative treatment group, the adjusted hazard ratio was 1.03 (95% CI: 0.21-5.19). It indicated that the observed survival in the conservative treatment group was about equal to its counterfactual counterpart: what it would be had if these men received radical prostatectomy. When weighting to the entire sample for this comparison, the hazard ratio was 0.81 (95% CI: 0.23-2.81). It resulted from the contrast between two counterfactual outcomes: what it would be if everyone received radical prostatectomy vs. what it would be if everyone received conservative treatment.

The diminished association when weighting to the conservative treatment is unlikely due to confounding because any unobserved risk factors are more likely to bias the results in favor of radical prostatectomy rather than conservative treatment. The variation in estimates from the different weighting methods possibly reflected a phenomenon of effect. That is, radical prostatectomy may benefit the population represented by the radical prostatectomy samples, but may not benefit the population represented by the conservative treatment samples. The effect modification can also be illustrated by the observed variation in propensity score quintile specific hazard ratios. Regardless of the additional HRQOL adjustment, radical prostatectomy was not associated with all-cause survival benefit for the first quintile with hazard ratios above 1.00. It was also noticed that nearly 50% conservatively treated men concentrated in the first quintile and nearly 50% definitively treatment men concentrated in the fifth quintile. This explained why the first quintile estimate dominated the overall estimation when weighting to the conservative treatment group, and the fifth quintile estimate dominated the overall estimation when weighting to the radical prostatectomy group.

Discrepancy from different confounding adjustment methods in the presence of effect modification was previously reported by Kurth[84] who estimated the effect of tissue plasminogen activator on mortality in stroke patients. They found that weighting to the whole study sample yielded an odds ratio of 10.77, while weighting to the treated group yielded an odds ratio of 1.11. The authors pointed out that the treatment effect was modified by treatment contraindications. Weighting methods with different target populations might produce strikingly different effect estimates when treatment contraindication was common in the untreated group but rare in the treatment group. Adjustment of propensity score as continuous covariate or quintile could not reveal the non-uniform effect.

In the context of localized prostate cancer treatment, short life expectancy can be considered as contraindications that modified the effect of radical prostatectomy. The 10-year life expectancy rule basically says radical prostatectomy offers survival benefit to men with at least 10-year Life expectancy but not to men with less than 10-year life expectancy. Although we do not have a specific life expectancy variable, the descriptive analysis had showed that men treated conservatively had multiple unfavorable characteristics, such as older age, more comorbidities, and worse HRQOL. These characteristics could collectively make radical prostatectomy ineffective. No such effect modification was observed for radiation therapy. All confounding adjustment methods yielded similar results. This was because the radiation therapy group had risk factor distributions very similar to those in the conservative treatment group. The quintile specific estimates were also fairly homogeneous with all hazard ratios below 1.00.

Comparison with Previous Studies

Wong[18] compared definitive treatment vs. expectant management in the SEER-Medicare population. Comprehensive sociodemographic and clinical variables at baseline were controlled by adjusting propensity score as a continuous covariate. They reported an adjusted hazard ratio of 0.69 (95% CI: 0.66-0.72) for 10-year all-cause mortality and an adjusted hazard ratio of 0.67 (95% CI: 0.58-0.77) for 10-year prostate cancer specific mortality. The current study produced a hazard ratio of 0.44 (95% CI: 0.19-1.05) for all-cause mortality and a hazard ratio of 0.26 (95% CI: 0.06-1.14) for prostate cancer-specific mortality when using the same propensity score method to adjust a similar set of confounders.

Several reasons may explain why we observed stronger survival benefit than the reference study: 1) Wong excluded men treated with hormonal therapy. Due to the limited sample size in CaPSURE, we combined both expectant management and hormonal therapy to compare with the definitive treatment. The hormonal therapy group appeared to have more advanced prostate

cancer and worse health conditions than the expectant management group, which could make the definitive treatment appear more superior. 2) Wong identified primary treatment by using the ICD-9 and procedure codes in claims data within 6 months after diagnosis. The current study used a 9-month time window recommended by CaPSURE. The treatment type in CaPSURE was specified in urologist surveys, which is supposed to be more accurate than claims codes. Moreover, we found that 12 men received radical prostatectomy and 120 men received radiation therapy between the 7th month and 9th month after diagnosis, accounting for approximately 10% of the definitive treatment group. If the time to treatment pattern observed in CaPSURE was generalizable, the SEER-Medicare study misclassified approximately 10% definitively treated men into the expectant management group, which would have made the two comparison groups more similar, thus biased the treatment estimates towards the null. 3) Wong excluded men that died within 1 year after diagnosis while we did not use such an exclusion criterion. They claimed that more expectant management men were excluded due to this reason than definitive treatment men, which favored the expectant management group.

Liu[19] separately compared different definitive treatments with expectant management in SEER-Medicare men aged 65-75 years old. Baseline sociodemographic and clinical factors were adjusted by using multivariate Cox regression model. When radical prostatectomy was used alone, the adjusted hazard ratio for 10-year all-cause mortality was 0.31 (95% CI: 0.25-0.37). When radical prostatectomy was combined with radiation therapy, the hazard ratio was 0.38 (95% CI: 0.28, 0.52). When radiation therapy was used alone, the hazard ratio was 0.68 (95% CI: 0.56-0.81). Our study yielded similar results when adjusting the reference propensity score. After further adjusting the baseline HRQOL variables, the radical prostatectomy associated all–cause survival benefit was attenuated with the hazard ratio was 0.46 (95% CI: 0.14-1.52). When

comparing between radiation therapy and expectant management, we yielded a lower hazard ratio of 0.47 (95% CI: 0.21-1.06). Again, Liu used the 6-month time window for primary treatment determination, which might had misclassified 10% radiation therapy patients into the expectant management group and biased their estimates towards the null.

Compared with the previous studies, our study has several advantages: 1) we controlled for a number of baseline HRQOL variables in addition to comprehensive sociodemographic and clinical factors. 2) more importantly, we evaluated the treatment effects in clearly defined target populations by using the weighting methods, and revealed that radical prostatectomy might not be associated with survival benefit in the conservative treatment group had if these patients were treated with radical prostatectomy. The previous studies provided a single estimate without clearly defined target population, which automatically hide the treatment effect heterogeneity. It might result in a misleading perception that radical prostatectomy was superior to conservative treatment regardless of patient characteristics. 3) we would argue that it may not be appropriate to assess the effectiveness of radical prostatectomy and radiation therapy as a whole, since these two treatment populations have very distinct characteristics.

Limitations

The present study had several limitations. First, the observational nature made the current study inevitably vulnerable to unmeasured confounding. No firm conclusion can be made regarding treatment superiority before large scale randomized trials are conducted.

Secondly, approximately 70% of the CaPSURE participants do not have baseline HRQOL data available. Previous study showed that inability to complete the SF-36 questionnaire by older people was associated with poor physical and mental functioning.[94] Physical and mental functioning are both key HRQOL domains. The missing data mechanism is therefore “missing not at random” and cannot be imputed correctly without additional information. These patients

had to be excluded from the current study. Completion of long health questionnaire is a selection process. Men included in our study are presumably healthier than the general prostate cancer population. Thus, the generalizability of the current study may be limited.

Thirdly, we might underestimate the confounding effect of the baseline HRQOL due to several study limitations. The dichotomization of HRQOL might lead to oversimplification. Subtle yet important health information might be omitted. The exclusion of men whose physical and mental status was too poor to complete the survey might reduce the variations of HRQOL in the study sample. The confounding effect of HRQOL is likely to be more pronounced in the general prostate cancer population. Nevertheless, these limitations are inherent in observational studies, reflecting the difficulties in observing and quantifying confounding variables.

Lastly, we used statistical models to account for uncertainties from missing data and informative censoring. We also used propensity score model and weighting model to control for the baseline confounding. The validity of the current study highly depends on the validity of the model assumptions, such as missing at random, censoring at random, correct model specification etc. Given the data we had, some of these assumptions could not be validated.

Summary and Conclusions

Our study suggests that HRQOL is strongly associated with primary treatment selection in elderly men diagnosed with localized prostate cancer. Men treated with radical prostatectomy have significantly better HRQOL than men treated alternatively. Men treated with radiation therapy have moderately better HRQOL than men treated conservatively. The associations are more pronounced for physical health related HRQOL domains than the mental health domains. These findings are consistent with the current prostate cancer treatment guideline that definitive treatment is recommended to men with good health status and long life expectancy.

Selection of relatively healthy patients for definitive treatment causes strong confounding in observational studies assessing primary treatment effectiveness with regard to all-cause mortality. Our study shows that additional adjustment of dichotomized HRQOL variables besides commonly considered confounders is methodologically desirable in observational studies. However, the improvement in confounding reduction appeared to be insufficient. The implausible association between definitive treatment and lower other-cause mortality remained strong, indicating the persistence of substantial residual confounding. The effectiveness of definitive treatment tends to be overestimated. Randomized trials are warranted to evaluate the efficacy of primary treatment for localized prostate cancer.

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