

PREDICTING OTHER CAUSE MORTALITY RISK FOR OLDER MEN WITH  
LOCALIZED PROSTATE CANCER

A Dissertation Presented

By

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PREDICTING OTHER CAUSE MORTALITY RISK FOR OLDER MEN WITH  
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## ABSTRACT

**Background:** Overtreatment of localized prostate cancer (PCa) is a concern as many men die of other causes prior to experiencing a treatment benefit. This dissertation characterizes the need for assessing other cause mortality (OCM) risk in older men with PCa and informs efforts to identify patients most likely to benefit from definitive PCa treatment.

**Methods:** Using the linked Surveillance Epidemiology and End Results-Medicare Health Outcomes Survey database, 2,931 men (mean age=75) newly diagnosed with clinical stage T1a-T3a PCa from 1998-2009 were identified. Survival analysis methods were used to compare observed 10-year OCM by primary treatment type. Age and health factors predictive of primary treatment type were assessed with multinomial logistic regression. Predicted mortality estimates from Social Security life tables (recommended for life expectancy evaluation) and two OCM risk estimation tools were compared to observed rates. An improved OCM prediction model was developed fitting Fine and Gray competing risks models for 10-year OCM with age, sociodemographic, comorbidity, activities of daily living, and patient-reported health data as predictors. The tools' ability to discriminate between patients who died and those who did not was evaluated with Harrell's c-index (range 0.5-1), which also guided new model selection.

**Results:** Fifty-four percent of older men with localized PCa underwent radiotherapy while 13% underwent prostatectomy. Twenty-three percent of those treated with radiotherapy and 12% of those undergoing prostatectomy experienced OCM within 10 years of treatment and thus were considered overtreated. Health factors indicative of a shorter life expectancy (increased comorbidity, worse physical health, smoking) had little to no association with radiotherapy assignment but were significantly related to

reductions in the likelihood of undergoing prostatectomy. Social Security life tables overestimated mortality risk and discriminated poorly between men who died and those who did not over 10 years (c-index=0.59). Existing OCM risk estimation tools were less likely to overestimate OCM rates and had limited but improved discrimination (c-index=0.64). A risk model developed with self-reported age, Charlson comorbidity index score, overall health (excellent-good/fair/poor), smoking, and marital status predictors had improved discrimination (c-index=0.70).

**Conclusions:** Overtreatment of older men with PCa is primarily attributable to radiotherapy and may be reduced by pretreatment assessment of mortality-related health factors. This dissertation provides a prognostic model which utilizes a set of five self-reported characteristics that better identify patients likely to die of OCM within 10 years of diagnosis than age and comorbidity-based assessments alone.

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## **LIST OF ABBREVIATIONS**

ADL - Activities of Daily Living

AIC - Akaike's Information Criterion

CaPSURE - Cancer of the Prostate Strategic Urologic Research Endeavor

CCI - Charlson Comorbidity Index

CMS - Centers for Medicare and Medicaid Services

COPD - Chronic Obstructive Pulmonary Disease

IRB - Institutional Review Board

MCS - Mental Component Score

MHOS - Medicare Health Outcomes Study

OCM - Other Cause Mortality

PCa - Prostate Cancer

PCOS - Prostate Cancer Outcomes Study

PCS - Physical Component Summary

PCSM - Prostate Cancer (Pca)-Specific Mortality

PF - Physical Functioning

PF-ADL - Physical Functioning Activities of Daily Living Composite Scale

PSA - Prostate Specific Antigen

SEER - Surveillance Epidemiology and End Results

SF-36 - Short Form-36 Health Survey

SRH - Self-Ratings of Health

VR-12 - Veteran's 12 Item Health Survey

## PREFACE

Publications related to this study but not presented in detail in this thesis are:

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## CHAPTER I: INTRODUCTION

Prostate cancer (PCa) is the most common non-skin cancer in American men; nearly one in six men are diagnosed over a lifetime.<sup>1</sup> Despite the high incidence of PCa, less than 16% of those diagnosed will die of their cancer; the vast majority of men with PCa ultimately die from other causes.<sup>2,3</sup> This is largely due to two factors; first, most men are diagnosed with PCa over the age of 65, and second, the majority of new PCa diagnoses (81%) are for lower-risk tumors that are confined to the prostate and tend to have a relatively indolent course.<sup>4,5</sup> Furthermore, randomized clinical trial data demonstrate a lack of treatment benefit over follow-up periods less than 8-10 years, when compared to conservatively managed controls.<sup>6</sup> Thus, guidelines recommend that clinicians routinely consider life expectancy when recommending management strategies for clinically localized PCa and that definitive treatments only be considered if overall life expectancy is >10 years.<sup>7-9</sup>

For men with prostate-confined tumors, the average risk of dying of PCa in the 10 years following diagnosis is less than 5%, regardless of treatment.<sup>10,11</sup> In contrast, the risk of dying of other non-PCa causes in 10 years can range from just 6% to over 90% depending on an individual's age, health, and social factors.<sup>10,12-15</sup> Thus, accurate assessment of 10-year life expectancy, and particularly the risk of dying of non-prostate causes, is essential for promoting appropriate treatment decision-making for men with PCa.

### **Current Utilization of Life Expectancy Evaluation in Clinical Practice**

Despite recommendations to routinely consider life expectancy in treatment decision-making for men with PCa less than 23% of PCa specialists in the U.S. utilize tools to estimate 10-year mortality risk.<sup>16</sup> This is a uniquely low utilization rate given that,

in contrast, over 80% of prostate cancer specialists rely on tools to classify the risk of prostate tumor recurrence.<sup>16</sup> The limited utilization of mortality risk estimation tools may be attributable to the lack of validated and endorsed methods for evaluating other cause mortality (OCM) risk.<sup>17</sup> Formal evaluations of the performance of these tools are needed to promote and inform clinical adoption.

Without the use of prediction tools, clinicians' independent estimates of life expectancy are often inaccurate.<sup>18–20</sup> In the absence of standardized routine consideration of mortality risk many patients likely receive definitive treatments only to go on to die of other causes within the 10 years following PCa treatment. These men likely do not experience any survival benefit from their PCa treatment and are thus considered overtreated.

### **The Problem of Prostate Cancer Overtreatment**

Studies increasingly present evidence of the overtreatment of patients with low-risk prostate cancer and have suggested that substantial percentages of patients receive definitive therapies who ultimately die of other causes in less than 10-years.<sup>12–15,21,22</sup> Available PCa management options can broadly be categorized into definitive (e.g., surgical or radiation therapies) or conservative management strategies (e.g., watchful waiting or active surveillance). Definitive treatments are provided with curative intent, and include radical prostatectomy, a surgical procedure which can be performed with open surgery, laparoscopy, or with robotic laparoscopy. There are also radiation therapies that include external beam radiation or brachytherapy. These definitive therapies are, however, often associated with side effects that can impair quality of life.<sup>23</sup> Thus, for individuals who are unlikely to experience any survival benefit from treatment of low to moderate-risk tumors, surgical or radiation therapies may result in harm.

However, more accurate life-expectancy evaluation is also critical for the few individuals who are undertreated for PCa, sometimes simply due to their age alone.<sup>21</sup> Better assessment of OCM risk will enable more appropriate allocation of treatment, improving both over and undertreatment.

Studies evaluating patient-level health factors and assignment to PCa therapies have demonstrated that factors such as comorbidity may not influence allocation to definitive therapy.<sup>14</sup> However, there has been some indication that radical prostatectomy is less likely to be offered to patients with higher comorbidity burden.<sup>21</sup> Recent work has supported a potential differential effect in the impact of age and comorbidity on radiotherapy and radical prostatectomy assignment.<sup>24</sup> Developing an improved understanding of the life expectancy-related health factors that currently influence treatment assignment is of high importance for identifying areas for improving patient selection for definitive therapy. Understanding how these factors may differently affect the likelihood of undergoing radiation or radical prostatectomy will help in providing tailored interventions for reducing overtreatment of PCa.

As overtreatment of PCa may be a heterogeneous phenomenon, understanding the extent to which the mainstays of therapy (radiation and radical prostatectomy) individually contribute to overtreatment is important. That older patients tend to receive radiotherapy more often than radical prostatectomy suggests there may be differences in the rates of overtreatment between these two treatment modalities.<sup>12,21,24</sup> Better characterization of these differences will provide high priority areas of intervention for improving patient selection for PCa treatment.

### **Current Risk Calculation Tools for Predicting Mortality in Prostate Cancer**

The National Comprehensive Cancer Network guidelines have recommended that clinicians utilize the Social Security life tables for evaluating overall life expectancy in patients diagnosed with PCa.<sup>9,25</sup> These life tables are based on data from males in the general US population and provide a simple age-based assessment of overall life expectancy. Overall life expectancy, however, is only a proxy for estimating OCM risk. While the Social Security life tables have been endorsed for overall life expectancy estimation, whether they provide accurate and clinically useful mortality estimates in men with localized PCa requires investigation.

Ideally, risk estimation tools would provide personalized, separate estimates of the risk of OCM that could be compared to the risk of dying of PCa-specific mortality (PCSM), which would allow patients to weigh the competing risks side-by-side.<sup>26</sup> To address this need tools have been developed to specifically estimate OCM risk in men with PCa. Currently, two nomograms (visual aids for estimating patient risk based on a limited of patient characteristics) are available for clinical use in specifically predicting the risk of OCM in patients with PCa.<sup>26,27</sup> There are also two life tables (look-up tables that classify patients into general risk categories) for OCM risk estimation.<sup>10,12</sup> While several risk estimation tools exist for evaluating OCM risk (Table 1.1), these tools require validation and no tools have been endorsed for clinical use.<sup>17,28</sup> Further, whether these OCM risk estimation tools, developed in populations of men with localized PCa, can provide improved estimates over Social Security life tables has yet to be determined.

### **Predictors of Other Cause Mortality in Prostate Cancer**

A growing body of literature has evaluated predictors of OCM for patients with PCa. Evidence consistently demonstrates that older age and a higher comorbidity



burden are strongly predictive of OCM.<sup>10,12,26,29–33</sup> Specified either as simple counts or weighted indices, such as the Charlson Comorbidity Index (CCI), comorbidity plays an important role in OCM prediction.<sup>29,34</sup> However, age and comorbidity alone are not complete determinants of mortality risk.

Studies of the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) and Prostate Cancer Outcomes Study databases (PCOS) have suggested there is value in incorporating sociodemographic and patient-reported health measures in OCM prediction models.<sup>27,33</sup> Variables such as education level, marriage and race have been associated with OCM risk.<sup>26,27,33</sup> Additionally, smoking is an important health behavior associated with OCM risk.<sup>33</sup> Among patient-reported measures of health, there is broad evidence to support the use of simple single-item self-ratings of health (SRH) from excellent to poor,<sup>20,27,35–37</sup> as well as more complex patient-reported measures of functional health and well-being, such as the Short Form-36 Health Survey (SF-36) for mortality risk estimation.<sup>20,33,37–41</sup> These self-ratings of health have been well validated in heterogeneous populations, including the Medicare managed care population and in patients with varying levels of comorbidities.<sup>42–46</sup> The SF-36 Physical Component Summary (PCS) score and its subdomains have been consistently associated with mortality in heterogeneous settings over a variety of time spans from 1 month to 10 years.<sup>37–39,47</sup>

While these many factors serve as important predictors of OCM in separate models, no prediction tool has yet to incorporate these elements into a single model. Such a comprehensive prediction tool may provide meaningful improvements in the accuracy of risk predictions and the ability to distinguish patients who are likely to die of OCM within 10-years and those likely to survive.

## **Specific Aims**

This dissertation aims to characterize the need for OCM risk estimation in older men newly diagnosed with localized PCa and aims to inform efforts to better identify older patients who would most likely benefit from aggressive treatment vs. those who may not, as they may be more likely to die of OCM. This work utilized data from the linked Surveillance Epidemiology and End Results - Medicare Health Outcomes Study (SEER-MHOS) database which contains detailed cancer and treatment information, cause of death, comorbidities, patient-reported physical and mental health, activities of daily living, and sociodemographic data on 19,727 men, mostly age 65 and older, undergoing all types of PCa management in diverse regions of the United States.<sup>48</sup> This dataset enables characterization of overtreatment of PCa among older American men, as well as evaluation of and improvement upon the performance of OCM prediction tools using statistical techniques to assess predictive model performance. It also supports the development of a novel prediction tool that better predicts personalized risk of 10-year OCM.<sup>49,50</sup> Specific aims of this dissertation are:

**Aim 1.** Define the extent of PCa overtreatment by treatment type and assess factors associated with assignment to particular treatment modalities among older men.

**1.1** Explore observed rates of 10-year OCM by definitive PCa treatment type.

**1.2** Explore whether age and health factors, predictive of dying of OCM, predict receipt of primary surgery or radiotherapy for prostate cancer in older American men.

**Aim 2.** Evaluate the performance of two tools for estimating 10-year OCM risk against Social Security life table estimates, which guidelines currently recommend for life-expectancy estimation.

**2.1** Evaluate the accuracy of mortality risk estimates vs. observed mortality rates in the SEER-MHOS data.

**2.2** Evaluate the risk estimation tools' ability to discriminate between individuals in the SEER-MHOS data who die and those who do not.

**Aim 3.** Develop an improved prediction model for 10-year OCM risk utilizing an efficient combination of self-reported data from men newly diagnosed with localized prostate cancer.

**3.1** Build a new model with improved discrimination between those who die of OCM and those who do not, exploring combinations of age, comorbidity, patient-reported health, smoking, and sociodemographic predictors, including effect modification by patient-reported health, comorbid conditions, and smoking.

**3.2** Create a prototype risk calculation tool to enable estimation of individualized 10-year OCM risk.

**Table 1.1: Previously published prediction models for other cause mortality and all-cause mortality risk for men with PCa and availability as a risk estimation tool**

| Publication First Author                     | Outcome Estimated           | Predictors  | Clinical Tool Available                                   |
|--|-----------------------------|---|---|
| Kutikov <sup>26</sup>                        | 10-year OCM                 | <ul style="list-style-type: none"> <li>• Age at diagnosis</li> <li>• Comorbidity count</li> <li>• Treatment with radiotherapy vs. radical prostatectomy</li> <li>• Receipt of androgen deprivation therapy</li> <li>• Race (black vs. white)</li> </ul>   | Nomogram for 10-year OCM risk                             |
| Daskivich <sup>12,30,31</sup>                | 10-year OCM                 | <ul style="list-style-type: none"> <li>• Age at diagnosis</li> <li>• Charlson Comorbidity Index score or comorbidity count</li> </ul>   | Two separate life tables for 10-year OCM risk estimation  |
| Hoffman <sup>27,*</sup>                      | 10-year OCM                 | <ul style="list-style-type: none"> <li>• Age at diagnosis</li> <li>• Self-rated general health (excellent/v. good/good/fair-poor)</li> <li>• Race/ethnicity (Hispanic vs. white vs. black)</li> </ul>   | Nomogram for 10-year OCM risk                             |
| Simone <sup>33</sup>                         | 5-year OCM                  | <ul style="list-style-type: none"> <li>• Age &gt;65 at diagnosis</li> <li>• SF-36 Physical Function ½ standard deviation below age-adjusted norm</li> <li>• Other malignancy at diagnosis</li> <li>• Smoker at diagnosis</li> <li>• Education level high school or less</li> <li>• High D'Amico risk group</li> </ul> | None  |
| Social Security Administration <sup>25</sup> | 10-year all-cause mortality | <ul style="list-style-type: none"> <li>• Age</li> </ul>   | Life tables and annual risk of all-cause mortality by age |
| Walz <sup>51</sup>                           | 10-year all-cause mortality | <ul style="list-style-type: none"> <li>• Age at therapy</li> <li>• Charlson Comorbidity Index score</li> </ul>  | Nomogram for 10-year all-cause mortality                  |
| Tewari <sup>52</sup>                         | 10-year non-PCa mortality   | <ul style="list-style-type: none"> <li>• Age at diagnosis</li> <li>• Charlson Comorbidity Index Score 2 or more</li> <li>• Income in \$10,000s</li> <li>• Radical prostatectomy</li> </ul>  | Life-tables for 10-year all-cause mortality               |

OCM= other cause mortality

Nomograms are visual aids for graphically estimating risk scores; they convert equations to visual aids for calculating risk scores

Lifetables provide risk-estimates in the form of look-up tables and can account for a limited set of patient characteristics

\*The Hoffman nomogram was published during the writing phase of this dissertation and thus is only briefly evaluated in Chapter IV of this dissertation

## CHAPTER II: DEFINING THE EXTENT AND NATURE OF PROSTATE CANCER OVERTREATMENT IN OLDER MEN

### ABSTRACT

**Objective:** To better characterize the extent of prostate cancer (PCa) overtreatment among older American men by reporting 10-year other cause mortality (OCM) rates after primary surgical or radiotherapy and to assess health factors predictive of treatment modality.

**Methods:** Using the linked Surveillance Epidemiology and End Results-Medicare Health Outcomes Survey database, men newly diagnosed with clinical stage T1a-T3a PCa from 1998-2009 were selected. Observed cumulative incidence of 10-year OCM was compared across men treated with radical prostatectomy, radiotherapy (brachytherapy/external-beam radiation), and conservatively managed men. Predictors of primary treatment, including age, Charlson Comorbidity Index (CCI) score, patient-reported physical health, and smoking status, were assessed using multinomial logistic regression, adjusted for D'Amico risk score, county-level radical prostatectomy rates, year of diagnosis, education, and race.

**Results:** Of 2,425 men (median age=73), 13% underwent radical prostatectomy and 54% underwent radiotherapy. Observed 10-year cumulative incidence of OCM among radical prostatectomy, radiotherapy, and conservatively managed patients was 12%, 23%, and 31%, respectively. Men of increasing age, CCI score, worse physical health, and smokers were less likely to undergo radical prostatectomy ( $p<0.05$ ), yet only increasing age was associated with reduced odds of radiotherapy after multivariable adjustment.

**Conclusions:** While most older men with localized PCa undergo radiotherapy as primary treatment for their disease, nearly a quarter of these men are overtreated. In comparison, overtreatment is less common with radical prostatectomy, as patients with worse overall health are much less likely to receive surgery. There may be substantial benefit to improving patient selection for radiotherapies through increased pretreatment consideration of patients' comorbidities and physical health.

## INTRODUCTION

Despite the high incidence of prostate cancer (PCa) in the U.S., the majority of men are diagnosed with low-risk tumors and die of other causes.<sup>2</sup> Studies increasingly present evidence of the overtreatment of patients with low-risk PCa and have suggested that roughly half of older men with multiple comorbidities and limited life expectancies may be overtreated.<sup>12–15</sup> This study aims to better characterize the extent to which definitive therapies, namely radical prostatectomy and radiotherapies, contribute to the problem of overtreatment. While older patients are more likely to receive radiotherapies,<sup>12</sup> it has yet to be determined whether these patients are more likely to be overtreated than patients electing to undergo prostatectomy.

To reduce overtreatment, patients must be more carefully assessed before undergoing primary definitive PCa therapies.<sup>17</sup> Guidelines recommend that clinicians reserve definitive therapy for patients with at least a 10-year life expectancy as there is limited evidence for treatment benefit for individuals with shorter life expectancies.<sup>7,9,53</sup> Patients dying of other non-PCa causes within 10 years of a definitive primary treatment are thus generally considered overtreated. Despite guideline recommendations, only 23% of PCa specialists use currently available tools for estimating patients' life

expectancies,<sup>16</sup> suggesting that clinicians may not systematically assess their patients' health status and life expectancies when guiding therapeutic decisions.

As a prerequisite to improving patient selection for treatment, our understanding of the current impact of patient-level health factors on treatment assignment must be improved. Prior population-based studies suggest that factors such as comorbidity burden have not meaningfully influenced patients' receipt of definitive PCa therapies.<sup>12,13</sup> Characterizing systematic differences in the extent to which health factors predict receipt of radical prostatectomy versus radiotherapies for PCa will aid in identifying health factors that can be emphasized for improving treatment decisions.

This population-based study sought to better characterize the extent of PCa overtreatment by determining 10-year other cause mortality (OCM) rates by treatment type. In addition, this study assessed whether age and important health-related factors predict the receipt of primary radical prostatectomy or radiotherapy among older American men.

## **METHODS**

### **Data Source**

Data were obtained from the Surveillance, Epidemiology, and End Results-Medicare Health Outcomes Survey (SEER-MHOS) linked database available through permission from the National Cancer Institute.<sup>48</sup> The SEER program's regional registries collect sociodemographic, tumor, and treatment data representative of 26% of the U.S. population.<sup>54</sup> The Centers for Medicare & Medicaid Services (CMS) annually surveys a sample of Medicare managed care participants (19% of all Medicare beneficiaries) to collect self-reported functional health and wellbeing, comorbidity, and health behavior

data with response rates ranging from 64-72%.<sup>48</sup> From 1998-2011 over 1.6 million Medicare enrollees completed MHOS surveys.<sup>55</sup> SEER and MHOS databases were linked through a collaboration between the National Cancer Institute and CMS with details previously described.<sup>48</sup> Follow-up survival data were available through SEER until February 2013.

### **Study Population**

Eligible participants were aged <80 when newly diagnosed with PCa between January 1, 1998 and December 31, 2009, and completed an MHOS survey within the 3 years preceding their PCa diagnosis. The population was restricted those aged <80 at diagnosis as this study intended to evaluate the impact of health factors on treatment assignment among older patients, but for whom age alone may not have ruled out aggressive therapy; few men over age 80 have a life expectancy greater than 10 years.<sup>12</sup> Patients diagnosed with PCa on autopsy or death certificate or with regionalized or metastasized tumors (clinical stage >T3a) were excluded.

For the analysis of predictors of treatment assignment, the population was limited to men diagnosed after January 1, 2004 as data on PSA values and Gleason scoring, necessary for more accurate risk stratification of tumors, was only available after this date in SEER.

### **Outcome Ascertainment**

Survival data and primary cause of death were ascertained through the SEER dataset. Patients not alive at last follow-up were classified as having died of PCa-specific or other non-prostate causes using the SEER cause of death recode variable (codpub). Patients who did not die within 10 years of PCa diagnosis were censored at 10 years if followed  $\geq 10$  years after diagnosis, or at time of last SEER follow-up if followed <10



years. Survival time was calculated from the date of diagnosis until the date of death, or censored at date of last SEER follow-up.

SEER collects treatment information on patients' primary treatment for PCa. Patients who underwent radical prostatectomy were considered to have received primary surgical therapy and patients undergoing brachytherapy, external beam radiation, or a combination of the two were classified as having received primary radiotherapy. Patients who underwent radical prostatectomy and additionally underwent some form of radiotherapy were classified as having received primary radical prostatectomy. Treatment variables in the SEER database have been validated against Medicare claims in patients with PCa, demonstrating >85% sensitivity and >94% specificity for radiotherapies and >86% agreement with Medicare data for receipt of surgical therapies.<sup>56,57</sup> Patients not receiving these primary therapies were considered conservatively managed, which may have included active surveillance, watchful waiting, and androgen deprivation therapy (all not documented in SEER), as well as any alternatives to mainstream definitive therapies (e.g. cryotherapy), although these alternatives were rarely administered.

### **Data Collection**

Specific health factors were selected from previously developed prediction models for estimating life expectancy or non-PCa mortality risk (Table 1.1); these included age at diagnosis, Charlson Comorbidity Index (CCI) score, patient-reported physical health, and smoking status. A CCI score was approximated using Charlson weights for 8 self-reported conditions in the MHOS (myocardial infarction, congestive heart failure, stroke, chronic obstructive pulmonary disease, diabetes, inflammatory bowel disease/ulcer, paralysis, other cancer), which are included in the CCI.<sup>34</sup> Self-

reported physical health was measured with the Physical Component Summary (PCS) score derived from two health-related quality of life surveys included in the MHOS: the SF-36 Health Survey (v1)<sup>42,43</sup> for men surveyed before 2006, and the VR-12 Health Survey<sup>58</sup> for men surveyed in 2006 and after. PCS scores were provided by MHOS and used a scoring algorithm that maximized comparability of scores across different survey forms.<sup>59</sup> Scores are normalized to a mean of 50 points in the general U.S. population with a standard deviation of 10 points, with higher scores representing better health.<sup>60</sup> Self-reported current smoking status (every day or some days) was determined from MHOS. Individuals who had unknown smoking status were categorized as non-smokers, as exploratory analyses revealed they experienced survival similar to non-smokers. Education was categorized as “more than a high school education” or “high school education or less” to provide consistency with prior definitions.<sup>33</sup> Race, reported in SEER, was categorized as white, black, Hispanic, Asian/Pacific Islander, and other.

SEER extent of disease (EOD) codes were utilized to identify tumors as clinical stage cT1, cT2, cT1/T2 or cT3a (for tumors 2004 and later). Tumor grade was characterized as well, moderately, or poorly differentiated. For patients diagnosed after January 1, 2004, D’Amico tumor risk group was assigned using clinical T-stage, pre-diagnosis PSA level, and Gleason score.<sup>61</sup> Patients missing one or more data elements for D’Amico risk stratification were assigned to the highest risk category based on available data, as these patients have similar tumor characteristics to those with complete SEER data.<sup>62</sup> Adjustment for regional variations in rates of administered definitive therapy, considered an important potential factor influencing treatment assignment, was achieved by accounting for the ratio of county-level radical prostatectomy rates from the Dartmouth Atlas of Health Care to the national average,

averaged over the period 2004-2007.<sup>63</sup> When county-specific information was not available, state-level radical prostatectomy rates were substituted. Subjects were matched to their SEER county of cancer diagnosis.

### **Statistical Analysis**

Observed cumulative incidence distributions for 10-year non-PCa death, accounting for the competing risk of prostate-specific mortality, were calculated for radical prostatectomy, radiotherapy, and conservatively managed groups.<sup>64</sup> A multinomial logistic regression model was fitted with treatment allocation as the outcome (conservative management [reference group] vs. radical prostatectomy vs. radiation therapy) and the age and health factor covariates listed above as predictors.<sup>65</sup> Models were adjusted for individuals' D'Amico risk group, Dartmouth Atlas ratio of county-level to national rate of prostatectomy, year of diagnosis, race, and education level, as these factors may influence the decision to undergo definitive therapy. The complete case method was used.

Several sensitivity analyses were performed to assess the robustness of the analyses. First, a multilevel multinomial logistic model was utilized to account for the clustering of observations within counties.<sup>65</sup> Second, the model was restricted to subjects with low and intermediate D'Amico risk tumors to assess for potential bias introduced by including individuals with high D'Amico risk tumors. Additionally, the cumulative incidence distributions of 10-year OCM by treatment type were recalculated including patients >80 years of age to assess potential underestimation of OCM rates. All reported p-values are two sided and a p-value of <0.05 was considered statistically significant. Analyses were performed with Stata 12 and SAS 9.3 software.

IRB exemption for this study was obtained from the University of Massachusetts Medical School and all work was performed under a data use agreement with the National Cancer Institute.

## RESULTS

Of the 19,727 patients with PCa in the SEER-MHOS database, 2,245 eligible patients were identified as having newly diagnosed cT1a-cT3a PCa from January 1, 1998 - December 31, 2009, and having completed an MHOS survey within 3 years preceding their PCa diagnosis. A subset of 1,316 patients diagnosed from January 1, 2004 - December 31, 2009 was identified for analysis of predictors of treatment assignment. Patient characteristics are detailed in Table 2.1, with characteristics of the smaller subset in Table 2.2. The majority (67%) of patients received primary definitive treatment during the observation period, with 13% of the total population receiving radical prostatectomy, and 54% receiving external beam radiation, brachytherapy, or a combination of these radiotherapies. Patients had a median age of 73 (IQR: 70-76) at diagnosis, with a broad range in comorbidity (CCI range: 0-7), and physical health (PCS range: 8-62) scores.

Observed cumulative incidence of 10-year OCM among radical prostatectomy, radiotherapy, and conservatively managed patients was 12%, 23%, and 31%, respectively. Figure 2.1 demonstrates the relationship between receipt of definitive therapies and increasing comorbidity burden and physical health.

All age and health factors were strongly associated with radical prostatectomy allocation, but relationships were weaker and often non-significant for radiotherapy (Table 2.3). Patients were significantly less likely to undergo both radical prostatectomy

and radiotherapies with each increasing year of age, but the association between age and prostatectomy was much larger than with radiotherapies (29% vs. 11% lower odds of treatment per year of age).

The studied health factors were negatively associated with the odds of undergoing radical prostatectomy. For each additional CCI point, patients had 39% lower odds of undergoing radical prostatectomy vs. conservative management. For every 10 points lower physical health patients had 34% lower odds of undergoing radical prostatectomy, while smokers were 54% less likely to undergo radical prostatectomy compared to conservative management. Higher CCI, worse physical health, and smoking were not associated with the odds of receiving radiotherapies (Table 2.3).

Patients with intermediate and high D'Amico risk tumors had over 3-and 20-fold increased odds of undergoing radical prostatectomy versus conservative management, respectively, as compared to patients with low D'Amico risk tumors; D'Amico tumor risk had weaker associations with undergoing radiotherapy (Table 2.3). Patients who were diagnosed with PCa in counties where radical prostatectomy is conducted at twice the national rate were almost twice as likely to receive prostatectomy versus conservative management. Conversely, patients were 45% less likely to receive radiotherapy versus conservative management in counties where radical prostatectomy was twice the national rate (Table 2.3).

Findings remained substantially similar in the sensitivity analyses. After accounting for clustering of observations within county, model estimates were nearly identical to the primary analysis (Table 2.4). When the model was restricted to low and intermediate D'Amico risk patients, physical health had slightly weaker estimated association with receipt of radical prostatectomy and had a slightly stronger, statistically

significant, association with receiving radiotherapy (15% reduced odds of undergoing radiotherapy for 10 points lower PCS) (Table 2.5). Ten-year OCM rates also remained nearly identical for radical prostatectomy (12%) and radiotherapy (24%) treated patients when patients >80 years of age at diagnosis were included in the analysis (Supplement 2.A).

## DISCUSSION

This study sought to assess rates of PCa overtreatment among older men treated with radical prostatectomy or radiotherapy and to characterize the impact of health factors on the likelihood of receiving these therapies. In this population of older American men, overtreatment of PCa was far more likely among radiotherapy than radical prostatectomy treated patients. Most men were treated with radiotherapy (54%) and nearly a quarter of these men died from non-prostate causes within 10 years, suggesting considerable overtreatment. In comparison, only 12% of radical prostatectomy treated men died of non-PCa causes over the 10 years following treatment. Further, while indicators of worse health were associated with a reduced likelihood of surgery, they did not predict a reduced likelihood of undergoing radiation treatments. These findings suggest systematic differences in the rates of overtreatment as well as factors associated with treatment selection between surgical and radiotherapies. Less frequent consideration of health factors prior to radiotherapy may contribute to higher overtreatment rates among these patients.

The large negative impact of worsening health factors on the likelihood of undergoing prostatectomy, combined with the relatively low estimated 12% rate of overtreatment suggests there may be less room for improving the selection of patients

for surgical therapy. In contrast, there may be substantial benefit to emphasizing improvement of patient selection for radiotherapies, the most common treatment modality among older men. Furthermore, these findings are consistent with a recent study from the distinct SEER-Medicare database, which reported increasing age and comorbidity strongly reduced the likelihood of receiving radical prostatectomy for PCa but similarly found a lack of negative association between increasing comorbidity burden and radiotherapy assignment.<sup>24</sup>

This assessment of the extent of overtreatment for men with localized PCa yielded lower rates than previously reported in U.S. population-based cohorts.<sup>12,15,22</sup> Nonetheless, overtreatment rates remained substantial among radiotherapy treated patients, but were encouragingly much lower among radical prostatectomy treated patients. Restricting the analysis to those age <80 at diagnosis did not appear to explain the lower overtreatment rates reported here; 10-year OCM rates remained nearly identical for radical prostatectomy and radiotherapy treated patients in sensitivity analyses that included patients >80 years of age (Supplement 2.A). In contrast to this study, prior analyses of overtreatment have relied on predictions of mortality risk, potentially over predicting mortality, while this study used survival analysis methods to report the observed cumulative incidence of mortality.<sup>12,15</sup> Additionally, Medicare managed care participants are slightly healthier with lower mortality risk than similar aged Medicare fee-for-service patients, potentially reducing 10-year mortality rates, and thus the estimates of overtreatment reported here.<sup>66</sup> Furthermore, reports of 10-year OCM rates from a cohort of patients exclusively treated with radical prostatectomy in Europe, have revealed very similar observed 10-year OCM rates to that reported here for men undergoing prostatectomy.<sup>67</sup>

Most clinicians would expect that patients receiving radiotherapy for PCa are older, have higher comorbidity burden, and worse physical health than surgically treated patients, as they are likely less robust surgical candidates. However, regardless of treatment modality life expectancy should influence the treatment decision-making process. Yet, there were no significant relationships between health factors and radiotherapy assignment. It should be noted that in the sensitivity analysis of only patients with low/intermediate D'Amico risk tumors, physical health had a small, but significant negative influence on radiotherapy assignment. However, comorbidity burden and smoking status continued to have no association with radiotherapy assignment in sensitivity analysis.

Targeted policy and research interventions may be needed to improve decision-making surrounding radiotherapy assignment for PCa. Increased consideration of comorbidity burden, physical functioning, and smoking history, factors which currently have little association with receipt of radiotherapy, may improve patient selection. Decision aids may be a mechanism for promoting consideration of these factors, but existing tools have yet to incorporate individualized considerations of life expectancy.<sup>68</sup> Furthermore, available nomograms for estimating life expectancy require improvement and may not be reliable enough for individual patient-level decision making.<sup>69</sup>

Treatment decision-making is complex, and many factors influence treatment assignment beyond life expectancy. There may be differences in preference for conservative management vs. definitive therapy among PCa specialists.<sup>70</sup> This bias may influence the extent to which clinicians consider life expectancy and could partially explain differences in overtreatment rates between radiotherapy and prostatectomy treated patients. Financial incentives to perform particular interventions may also play a



role.<sup>22</sup> That county rates of prostatectomy from the Dartmouth Atlas predicted receipt of prostatectomy and radiotherapy also indicates that local biases towards particular interventions may influence treatment assignment.

This study is subject to limitations that may impact the generalizability of findings. While SEER data have been validated and demonstrate adequate sensitivity and specificity for radical prostatectomy and radiotherapy,<sup>56,57</sup> there remains potential for bias due to misclassification of treatment. However, treatment rates observed in this study were similar to rates from claims-based assessments of PCa treatment in older men over this same time period;<sup>24</sup> thus misclassification was likely minimal. Additionally, 10-year survival was calculated from date-of-diagnosis and thus approximated post-treatment survival, as exact date-of-treatment was not available. However, differences between diagnosis and treatment dates were less than 1 year as SEER records primary treatments administered within 12 months of diagnosis.<sup>48</sup> Finally, by opting not to predict 10-year OCM risk at diagnosis, and instead reporting observed OCM rates, there is some potential for misclassification of overtreatment. For example, patients dying of unpredictable causes after definitive PCa treatment may not be fairly characterized as overtreated, as clinicians could not be expected to reasonably have anticipated some of these outcomes (e.g. subsequent development of another primary cancer). However, given that existing OCM prediction models are very limited in their ability to discriminate between individuals who die and those who survive,<sup>69</sup> utilizing OCM predictions instead of observed rates may have potentially resulted in even greater rates of misclassification. Reporting observed 10-year OCM rates is an important component of understanding overtreatment and defining to what extent patients are prematurely dying prior to experiencing treatment benefit.

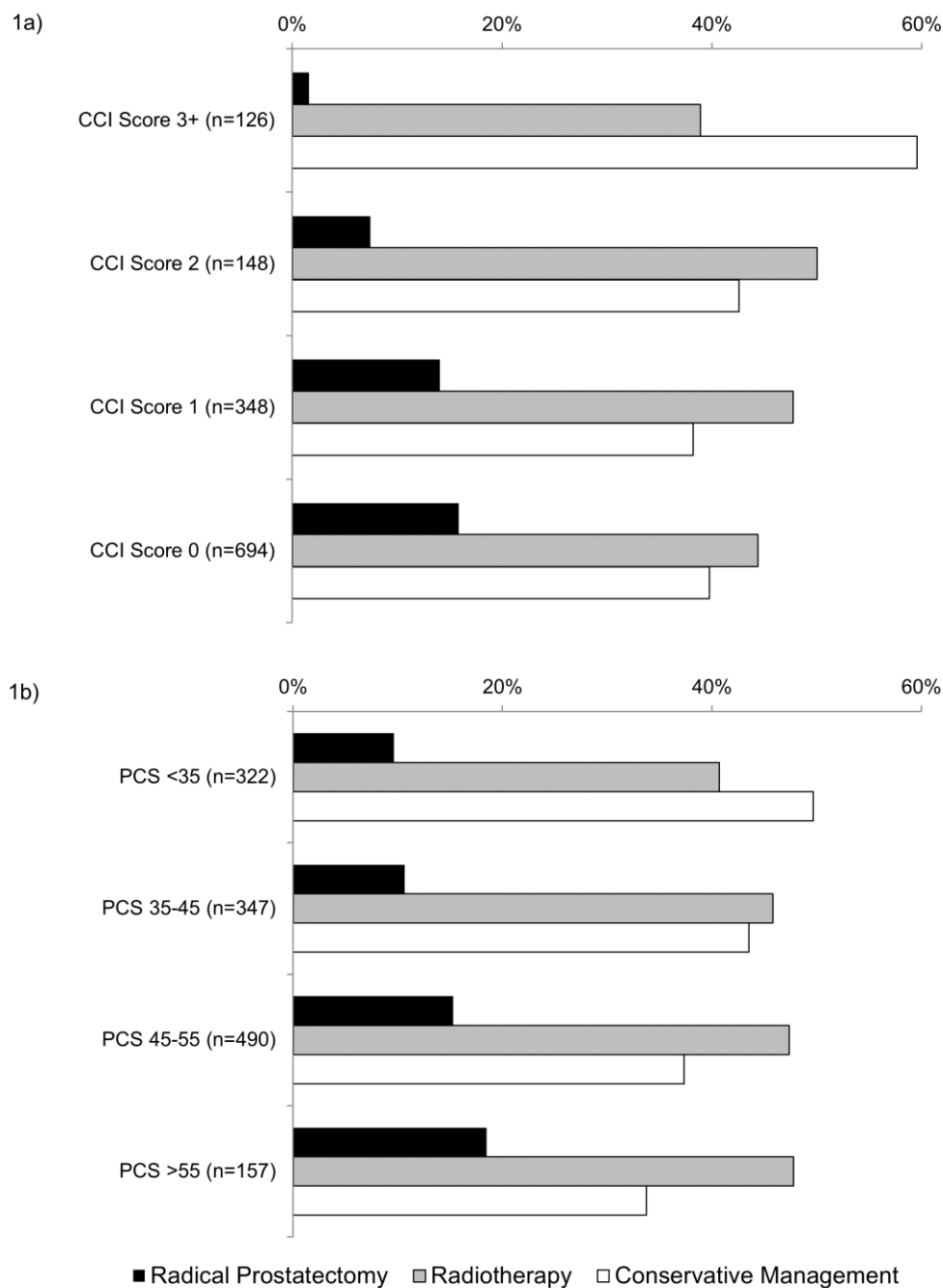
This study also has a number of strengths. The SEER-MHOS database allowed exploration of relationships with many validated health factors (e.g. comorbidity, physical health, and smoking) that have consistently been associated with OCM risk (Table 1.1). Thus it is unlikely that the lack of observed association between these factors and receipt of radiotherapy was due to poor specification of health status. Analyses were also adjusted for clinical factors that influence treatment assignment, summarized in the D'Amico risk score, and county-level variations in prostatectomy rates, both of which had important associations with treatment assignment.

## **CONCLUSIONS**

While most older men with localized PCa undergo radiotherapy as a primary treatment for their disease, nearly a quarter of these men are overtreated, dying of non-prostate causes within 10 years. In comparison, overtreatment with radical prostatectomy is less common, as worse overall health is associated with a reduced likelihood of receiving this treatment. Efforts are needed to improve patient selection for radiotherapy for PCa, particularly among older men with increasing comorbidity and limited physical health.

**Figure 2.1: PCa treatment utilization by comorbidity burden and physical health**

Percentage of patients diagnosed from 2004-2009 with  $\leq$ cT3a prostate cancer managed with primary radical prostatectomy, primary radiotherapy, or managed conservatively by worse to better **a)** Charlson Comorbidity Index (CCI) score **b)** Physical Health (PCS)



**Table 2.1: Patient characteristics at baseline by survival status at last follow-up**

|   | Total      | Prostate-Specific Death | Other Cause Mortality | Surviving  | p-value <sup>a</sup> |
|---|------------|-------------------------|-----------------------|------------|----------------------|
| <b>No. of patients (%)</b>                  | 2425       | 76 (3)                  | 465 (19)              | 1884 (78)  | -                    |
| <b>Mean age at diagnosis</b>                | 72.9       | 74.5                    | 73.8                  | 72.6       | <0.001               |
| <b>Race/ethnicity (%)</b>                   |            |                         |                       |            |                      |
| White                                       | 1879 (77)  | 57 (75)                 | 371 (80)              | 1451 (77)  | 0.282                |
| Black                                       | 290 (12)   | ~                       | 55 (12)               | 223 (12)   |                      |
| Hispanic/Asian/Pacific Islander or other    | 256 (11)   | ~                       | 39 (8)                | 210 (11)   |                      |
| <b>Charlson Comorbidity Index Score (%)</b> |            |                         |                       |            | <0.001               |
| 0   | 1326 (54)  | 31 (40)                 | 177 (38)              | 1118 (59)  |                      |
| 1   | 586 (24)   | 18 (24)                 | 130 (28)              | 438 (23)   |                      |
| ≥2  | 513 (21)   | 27 (35)                 | 158 (34)              | 328 (17)   |                      |
| <b>Patient-Reported Physical Health</b>     |            |                         |                       |            |                      |
| Mean PCS Score (IQR)                        | 44 (36-53) | 41 (32-53)              | 40 (30-51)            | 44 (38-53) | <0.001               |
| <b>Smoker at diagnosis (%)</b>              | 301 (12)   | 18 (24)                 | 86 (18)               | 197 (10)   | <0.001               |
| <b>Tumor Grade</b>                          |            |                         |                       |            | <0.001               |
| Well to Moderately Differentiated           | 1630 (67)  | 30 (39)                 | 338 (73)              | 1262 (67)  |                      |
| Poorly Differentiated or Unavailable*       | 795 (33)   | 46 (61)                 | 127 (27)              | 622 (33)   |                      |
| <b>Tumor Clinical T-Stage</b>               |            |                         |                       |            | <0.001               |
| cT1   | 1,193 (49) | 20 (26)                 | 227 (49)              | 939 (50)   |                      |
| cT2   | 819 (34)   | 34 (45)                 | 136 (29)              | 649 (34)   |                      |
| cT1/T2 or T3a or Unavailable**              | 413 (17)   | 22 (29)                 | 102 (22)              | 296 (16)   |                      |
| <b>Primary Prostate Cancer Management</b>   |            |                         |                       |            | <0.001               |
| Conservative                                | 794 (33)   | 46 (60)                 | 197 (42)              | 551 (29)   |                      |
| Radical Prostatectomy                       | 323 (13)   | ~                       | 28 (6)                | 294 (16)   |                      |
| Radiation Therapy                           | 1308 (54)  | ~                       | 240 (52)              | 1039 (55)  |                      |

<sup>a</sup> Patient characteristics were compared among those dying of prostate cancer, other causes, and survivors using one-way analysis of variance tests and chi-squared tests as appropriate.

~ exact n=, % not reportable per SEER-MHOS data use agreements as cell size <11 individuals for certain sub-categories

\*The small percentage of ungraded tumors were not reported individually in this table due to cell size reporting limitations and represented <3% of the total sample.

\*\*cT3a tumors contributed less than 2% to all categories; exact numbers were not reportable per SEER-MHOS data use agreements. Those without detailed cT-stage available (<3% of the sample) did not have regionalized/metastasized tumors, as confirmed by other SEER staging variables.

**Table 2.2: Characteristics of patients considered in multinomial logistic model for treatment allocation**

|   | <b>Total</b> | <b>Primary Radical<br/>Prostatectomy</b> | <b>Primary<br/>Radiotherapy</b> | <b>Conservative<br/>Management</b> | <b>p-value<sup>a</sup></b> |
|---|--------------|--|---------------------------------|------------------------------------|----------------------------|
| <b>No. of patients (%)</b>                              | 1,316        | 172 (13)                                 | 597 (45)                        | 547 (42)                           | -                          |
| <b>Mean age at diagnosis</b>                            | 75.1         | 70.5                                     | 74.2                            | 77.5                               | <0.001                     |
| <b>Race/ethnicity (%)</b>                               |              |  |                                 |                                    | <0.001                     |
| White   | 872 (66)     | 108 (63)                                 | 375 (63)*                       | 389 (71)                           |                            |
| Black   | 153 (12)     | 19 (11)                                  | 75 (13)                         | 59 (11)                            |                            |
| Hispanic  | 119 (9)      | 17 (10)                                  | 61 (10)                         | 41 (8)                             |                            |
| Asian/Pacific Islander or other~                        | 172 (13)     | 28 (16)                                  | 86 (14)*                        | 58 (10)                            |                            |
| <b>Charlson Comorbidity Index Score (%)</b>             |              |  |                                 |                                    | <0.001                     |
| 0   | 694 (53)     | 110 (64)                                 | 308 (52)                        | 276 (50)                           |                            |
| 1   | 348 (26)     | 49 (28)                                  | 166 (28)                        | 133 (24)                           |                            |
| ≥2  | 572 (21)     | 13 (8)                                   | 123 (20)                        | 138 (26)                           |                            |
| <b>Patient Reported Physical Health</b>                 |              |  |                                 |                                    |                            |
| Mean PCS Score (IQR)                                    | 43 (35-52)   | 45 (38-54)                               | 43 (36-52)                      | 41 (32-51)                         | <0.001                     |
| <b>Smoker at diagnosis (%)</b>                          | 152 (12)     | 18 (10)                                  | 76 (13)                         | 58 (11)                            | 0.47                       |
| <b>High school education or less (%)</b>                | 696 (54)     | 82 (48)                                  | 316 (54)                        | 298 (56)                           | 0.21                       |
| <b>D'Amico Risk (%)</b>                                 |              |  |                                 |                                    | <0.001                     |
| Low   | 476 (36)     | 21 (12)                                  | 221 (37)                        | 234 (43)                           |                            |
| Intermediate  | 422 (32)     | 29 (17)                                  | 228 (38)                        | 165 (30)                           |                            |
| High  | 418 (31)     | 122 (71)                                 | 148 (25)                        | 148 (27)                           |                            |
| <b>Mean ratio of county RP rate to national RP rate</b> | 0.98         | 1.06                                     | 0.93                            | 1.01                               | <0.001                     |

<sup>a</sup> Patient characteristics were compared among treatment groups using one-way analysis of variance tests and chi-squared tests as appropriate.

~ SEER-MHOS data use agreements do not allow reporting of cell sizes <11 individuals, thus for table 1 Asian/Pacific Islander and other race categories were reported as a combined group, although analyzed separately in multivariate analyses.

**Table 2.3: Adjusted multinomial logistic regression model predicting treatment allocation in 1268 patients with conservatively managed patients as the comparator group**

|   | Predictor   | Odds Ratio  | 95% Confidence Interval | p-value          |
|---|---|-------------|-------------------------|------------------|
| Radical Prostatectomy   | <b>Age at diagnosis (1 year increments)</b>                 | <b>0.71</b> | <b>0.67-0.75</b>        | <b>&lt;0.001</b> |
|   | <b>Comorbidity Score (CCI)</b>                              | <b>0.61</b> | <b>0.46-0.80</b>        | <b>&lt;0.001</b> |
|   | <b>Physical Health (PCS) 1 SD (10pts) lower</b>             | <b>0.66</b> | <b>0.52-0.84</b>        | <b>0.001</b>     |
|   | <b>Smoker at baseline</b>                                   | <b>0.46</b> | <b>0.23-0.95</b>        | <b>0.04</b>      |
|   | D'Amico risk intermediate vs. low                           | 3.00        | 1.55-5.79               | 0.001            |
|   | D'Amico risk high vs. low                                   | 19.70       | 10.91-35.57             | <0.001           |
|   | Race vs. white  |             |                         |                  |
|   | Black   | 1.07        | 0.53-2.18               | 0.84             |
|   | Hispanic  | 1.88        | 0.88-4.05               | 0.15             |
|   | Asian/ Pacific Islander                                     | 3.29        | 1.60-6.76               | <0.001           |
|   | Other cat.  | 0.50        | 0.12-2.00               | 0.33             |
|   | Education: high school or less                              | 1.11        | 0.70-1.75               | 0.66             |
|   | Year of diagnosis   | 1.04        | 0.92-1.17               | 0.57             |
|   | Ratio of county radical prostatectomy rate to national rate | 1.91        | 1.02-3.57               | 0.04             |
| Radiotherapy  | <b>Age at diagnosis (1 year increments)</b>                 | <b>0.89</b> | <b>0.87-0.91</b>        | <b>&lt;0.001</b> |
|   | <b>Comorbidity Score (CCI)</b>                              | <b>0.93</b> | <b>0.83-1.03</b>        | <b>0.17</b>      |
|   | <b>Physical Health (PCS) 1 SD (10pts) lower</b>             | <b>0.90</b> | <b>0.79-1.02</b>        | <b>0.11</b>      |
|   | <b>Smoker at baseline</b>                                   | <b>0.92</b> | <b>0.62-1.37</b>        | <b>0.70</b>      |
|   | D'Amico risk intermediate vs. low                           | 1.87        | 1.39-2.53               | <0.001           |
|   | D'Amico risk high vs. low                                   | 1.54        | 1.12-2.14               | 0.009            |
|   | Race vs. white  |             |                         |                  |
|   | Black   | 1.04        | 0.69-1.57               | 0.83             |
|   | Hispanic  | 1.54        | 0.97-2.45               | 0.07             |
|   | Asian/ Pacific Islander                                     | 1.61        | 1.02-2.55               | 0.04             |
|   | Other cat.  | 0.84        | 0.41-1.71               | 0.63             |
|   | Education: high school or less                              | 0.92        | 0.89-1.03               | 0.56             |
|   | Year of diagnosis   | 0.96        | 0.89-1.03               | 0.21             |
|   | Ratio of county radical prostatectomy rate to national rate | 0.55        | 0.37-0.83               | 0.004            |
| <p><b>Bold</b> typeface signifies factors previously associated with the risk of dying of non-PCa causes. In total, 168 men received radical prostatectomy, 576 received radiotherapy, and 524 were conservatively managed.<br/> <b>CCI:</b> Charlson Comorbidity Index<br/> <b>PCS:</b> Physical Component Summary score</p> |   |             |                         |                  |

**Table 2.4: Sensitivity analysis: Clustered multinomial logistic model predicting treatment allocation, clustered by county, with conservatively managed patients as the comparator group**

|  | Predictor   | Odds Ratio  | 95% Confidence Interval | p-value          |
|--|---|-------------|-------------------------|------------------|
| Radical Prostatectomy  | <b>Age at diagnosis (1 year increments)</b>                 | <b>0.70</b> | <b>0.66-0.74</b>        | <b>&lt;0.001</b> |
|  | <b>Comorbidity Score (CCI)</b>                              | <b>0.60</b> | <b>0.46-0.79</b>        | <b>&lt;0.001</b> |
|  | <b>Physical Health (PCS) 1 SD (10pts) lower</b>             | <b>0.67</b> | <b>0.52-0.85</b>        | <b>0.001</b>     |
|  | <b>Smoker at baseline</b>                                   | <b>0.47</b> | <b>0.22-0.97</b>        | <b>0.04</b>      |
|  | D'Amico risk intermediate vs. low                           | 2.92        | 1.51-5.66               | 0.002            |
|  | D'Amico risk high vs. low                                   | 20.39       | 11.21-37.08             | <0.001           |
|  | Race/ethnicity vs. white                                    |             |                         |                  |
|  | Black   | 1.03        | 0.50-2.14               | 0.93             |
|  | Hispanic  | 1.69        | 0.77-3.70               | 0.19             |
|  | Asian/ Pacific Islander                                     | 2.42        | 1.11-5.29               | 0.03             |
|  | Other cat.  | 0.47        | 0.12-1.87               | 0.28             |
|  | Education: high school or less                              | 1.08        | 0.68-1.71               | 0.76             |
|  | Year of diagnosis   | 1.04        | 0.93-1.17               | 0.51             |
|  | Ratio of county radical prostatectomy rate to national rate | 1.78        | 0.83-3.80               | 0.14             |
| Radiotherapy   | <b>Age at diagnosis (1 year increments)</b>                 | <b>0.88</b> | <b>0.86-0.91</b>        | <b>&lt;0.001</b> |
|  | <b>Comorbidity Score (CCI)</b>                              | <b>0.92</b> | <b>0.82-1.03</b>        | <b>0.16</b>      |
|  | <b>Physical Health (PCS) 1 SD (10pts) lower</b>             | <b>0.91</b> | <b>0.80-1.03</b>        | <b>0.14</b>      |
|  | <b>Smoker at baseline</b>                                   | 0.94        | 0.62-1.41               | <b>0.75</b>      |
|  | D'Amico risk intermediate vs. low                           | 1.81        | 1.33-2.47               | <0.001           |
|  | D'Amico risk high vs. low                                   | 1.60        | 1.14-2.24               | 0.007            |
|  | Race/ethnicity vs. white                                    |             |                         |                  |
|  | Black   | 1.01        | 0.65-1.57               | 0.95             |
|  | Hispanic  | 1.38        | 0.85-2.26               | 0.20             |
|  | Asian/ Pacific Islander                                     | 1.17        | 0.66-2.06               | 0.60             |
|  | Other cat.  | 0.75        | 0.36-1.58               | 0.45             |
|  | Education: high school or less                              | 0.90        | 0.68-1.19               | 0.46             |
|  | Year of diagnosis   | 0.96        | 0.92-1.10               | 0.15             |
|  | Ratio of county radical prostatectomy rate to national rate | 0.53        | 0.30-0.96               | 0.04             |
| <b>Bold</b> typeface signifies factors previously associated with the risk of dying of non-PCa causes. In total, 168 men received radical prostatectomy, 576 received radiotherapy, and 524 were conservatively managed.<br>CCI: Charlson Comorbidity Index<br>PCS: Physical Component Summary score |   |             |                         |                  |

**Table 2.5: Sensitivity analysis: low-intermediate D'Amico risk patients only: Multinomial logistic model predicting treatment allocation, in 858 patients, with conservatively managed patients as the comparator group**

|   | Predictor   | Odds Ratio  | 95% Confidence Interval | p-value          |
|---|---|-------------|-------------------------|------------------|
| Radical Prostatectomy   | <b>Age at diagnosis (1 year increments)</b>                 | <b>0.77</b> | <b>0.72-0.83</b>        | <b>&lt;0.001</b> |
|   | <b>Comorbidity Score (CCI)</b>                              | <b>0.66</b> | <b>0.44-0.98</b>        | <b>0.04</b>      |
|   | <b>Physical Health (PCS) 1 SD (10pts) lower</b>             | <b>0.76</b> | <b>0.54-1.07</b>        | <b>0.11</b>      |
|   | <b>Smoker at baseline</b>                                   | <b>0.26</b> | <b>0.06-1.19</b>        | <b>0.08</b>      |
|   | D'Amico risk intermediate vs. low                           | 2.63        | 1.51-5.66               | 0.003            |
|   | Race/ethnicity vs. white                                    |             |                         |                  |
|   | Black   | 0.76        | 0.24-2.44               | 0.65             |
|   | Hispanic  | 1.72        | 0.62-4.79               | 0.30             |
|   | Asian/ Pacific Islander                                     | 3.22        | 1.18-8.81               | 0.02             |
|   | Other cat.  | -           | -                       | -                |
|   | Education: high school or less                              | 0.72        | 0.37-1.39               | 0.33             |
| Radiotherapy  | <b>Age at diagnosis (1 year increments)</b>                 | <b>0.89</b> | <b>0.86-0.92</b>        | <b>&lt;0.001</b> |
|   | <b>Comorbidity Score (CCI)</b>                              | <b>0.97</b> | <b>0.85-1.11</b>        | <b>0.69</b>      |
|   | <b>Physical Health (PCS) 1 SD (10pts) lower</b>             | <b>0.85</b> | <b>0.74-0.99</b>        | <b>0.04</b>      |
|   | <b>Smoker at baseline</b>                                   | <b>0.92</b> | <b>0.58-1.47</b>        | <b>0.73</b>      |
|   | D'Amico risk intermediate vs. low                           | 1.85        | 1.37-2.51               | <0.001           |
|   | Race/ethnicity vs. white                                    |             |                         |                  |
|   | Black   | 1.01        | 0.63-1.62               | 0.97             |
|   | Hispanic  | 1.48        | 0.87-2.51               | 0.15             |
|   | Asian/ Pacific Islander                                     | 1.80        | 1.04-3.14               | 0.04             |
|   | Other cat.  | 0.88        | 0.38-2.06               | 0.78             |
|   | Education: high school or less                              | 0.84        | 0.62-1.15               | 0.28             |
|   | Year of diagnosis   | 0.93        | 0.86-1.01               | 0.11             |
|   | Ratio of county radical prostatectomy rate to national rate | 0.56        | 0.35-0.90               | 0.02             |
| <p><b>Bold</b> typeface signifies factors previously associated with the risk of dying of non-PCa causes. In total, 50 men received radical prostatectomy, 449 received radiotherapy, and 399 were conservatively managed.</p> <p>Note: This analysis was limited by sample size, with far fewer than 10 outcomes per covariate in the radical prostatectomy group.</p> <p>CCI: Charlson Comorbidity Index</p> <p>PCS: Physical Component Summary score</p> |   |             |                         |                  |



### **Supplement 2.A: Sensitivity Analysis: Re-estimation of 10-year cumulative incidence of other cause mortality by treatment type including patients >80 years of age at diagnosis**

Limiting the population in the main analysis of 10-year OCM rates by PCa treatment type to patients <80 years of age at PCa diagnosis may have biased the estimates of 10-year OCM downward, thus, a sensitivity analysis was performed. Cumulative incidence distributions of 10-year non-PCa death by treatment type were re-estimated including patients >80 years of age in the analysis to assess potential underestimation of OCM rates by excluding these patients from the main analysis.

The sample grew from 2,425 individuals in the main analysis to 2,931 men, by including those men over 80 years of age at PCa diagnosis. Mean age increased to 75 from 74. Recalculated cumulative incidence of 10-year OCM among radical prostatectomy, radiotherapy, and conservatively managed patients was 12%, 24%, and 38%, respectively. Thus, the estimates of 10-year cumulative incidence of OCM largely did not change for patients who underwent radical prostatectomy or radiotherapy. The estimate for conservatively managed men did, however, increase by 7%. The distributions of treatment assignment between the main analysis cohort and the sensitivity analysis cohort are detailed in Table 2A1. The vast majority of those over 80 years of age at diagnosis were conservatively managed (75%), with almost no patients receiving radical prostatectomy.

**Table 2.A.1: Number of patients by treatment type in the main analysis cohort and the sensitivity analysis**

| <b>Treatment Modality</b>  | <b>Main Analysis Cohort<br/>(2,425 patients)<br/>Number of Patients:</b> | <b>Sensitivity Analysis Cohort<br/>(2,931 patients)<br/>Number of Patients:</b> |
|--|--|---|
| Definitive Treatment:<br>Radical Prostatectomy or<br>Radiotherapy* | 1631 (67%)   | 1757 (60%)  |
| Conservative Management  | 794 (33%)  | 1174 (40%)  |

\*Due to SEER-MHOS data agreements the exact number of patients undergoing radical prostatectomy in the sensitivity analysis cohort cannot be reported, as the number of patients added to the main analysis cohort was <11, below the minimum reportable cell size. Thus, the number of radical prostatectomy or radiotherapy treated patients is reported as one category. The vast majority of patients added (75%) were conservatively managed.

## CHAPTER III: EVALUATION OF 10-YEAR OTHER CAUSE MORTALITY RISK ESTIMATES FOR MEN WITH PROSTATE CANCER

### ABSTRACT

**Objective:** To evaluate the performance of 10-year mortality risk estimates from the Social Security life tables, recommended by clinical guidelines for life-expectancy estimation in men with prostate cancer (PCa), as compared to newer tools for estimating other cause mortality (OCM) risk.

**Methods:** 2,931 men newly diagnosed with clinical stage T1a-T3a PCa from 1998-2009 were identified from the linked Surveillance Epidemiology and End Results - Medicare Health Outcomes Survey (SEER-MHOS) database with a median follow-up of 7.7 years. Predicted 10-year mortality risk from Social Security life tables, from an OCM risk estimation nomogram, and an OCM risk estimation table were compared to observed 10-year all-cause mortality and observed 10-year OCM rates across quintiles of patients with increasing predicted risk, with quintiles defined separately for each tool. Observed all-cause mortality rates were determined with Kaplan-Meier methods; observed OCM rates with cumulative incidence distributions for 10-year OCM. The prediction models' ability to discriminate between those who died and those who did not was evaluated with Harrell's c-index (range: 0.5-1.0).

**Results:** The Social Security method predicted 26% 10-year all-cause mortality among the lowest risk quintile of patients (vs. observed rate: 20%), and predicted 58% mortality for the highest risk quintile (vs. observed rate: 42%). Predicted OCM rates from the two OCM risk estimation tools were closer to observed rates. Among the lowest risk quintiles of patients the predicted OCM rates ranged from 14-22%, while observed OCM rates

were 14-15%. Among the highest risk quintiles of patients predicted OCM rates ranged from 46-57%, while observed OCM rates were 38-39%. Using Social Security estimates, discrimination between those who died and those who did not was poor (c-index: 0.59). OCM specific tools provided slightly improved discrimination (c-index: 0.64 for both tools).

**Conclusions:** OCM risk estimation tools evaluated in this study provided more accurate estimates of 10-year mortality rates and more optimally discriminated between individuals dying and surviving during this time period than Social Security life table estimates. However, these tools remain limited in their ability to distinguish between individuals who will die versus those who will not; thus they may have limited clinical utility.

## INTRODUCTION

Clinical care guidelines consistently recommend that definitive prostate cancer (PCa) therapies be reserved for patients with at least a 10-year life expectancy.<sup>7,9,53</sup> For the 100,000 men annually diagnosed in the U.S. with low-risk prostate cancers, regardless of treatment, the probability of dying from PCa within 10 years of diagnosis is less than 5%.<sup>10,11</sup> In contrast, the competing risk of dying of other non-PCa causes within 10 years of diagnosis can range from as little as 6% for the youngest and healthiest men to over 90% among older men with high comorbidity burden.<sup>10,12-15</sup> While accurately predicting this highly variable non-prostate mortality risk is important to life-expectancy estimation, less than one quarter of prostate cancer specialists routinely incorporate this into practice.<sup>16</sup>

One potential explanation for the limited adoption of life expectancy evaluation is the dearth of validated and endorsed evaluation methods.<sup>17,28</sup> The National Comprehensive Cancer Network guidelines have recommended utilization of the Social Security life tables for evaluating overall life expectancy for men with prostate cancer.<sup>9,25</sup> These life tables provide a simple age-based assessment of predicted life expectancy based on data from males in the general U.S. population. However, ideally, clinicians should incorporate more individualized assessments of their patients' health status in their estimations of life expectancy. Clinicians should also be able to determine the risk of other cause mortality (OCM) separately from PCa specific mortality (PCSM) risk.<sup>26</sup> To address these needs tools have been developed for clinical use to predict the risk of OCM in patients with PCa, incorporating assessments of patients' comorbidities (Table 3.1).<sup>7,10,12,26,27</sup> However, whether these risk estimation tools provide clinically useful determinations of life expectancy in men with localized PCa has yet to be determined.

To be useful in the clinic, risk estimation tools must be able to correctly discriminate between individual patients who will experience the predicted event and those who will not. These tools must also closely predict the observed rate of events across groups of patients with increasing risk. The present study evaluates whether two newer OCM risk estimation tools, specifically developed in populations of men with localized PCa, can substantially improve the accuracy of risk estimates and better discriminate between patients who die of OCM and those who do not, as compared to the existing Social Security life tables.

## **METHODS**

Predicted 10-year mortality risk estimates were compared from three different tools: (1) Social Security all-cause mortality estimates for men in the U.S. general population,<sup>71</sup> (2) a nomogram for predicting OCM risk developed in the Cancer of the Prostate Strategic Urologic Endeavor (CaPSURE) database,<sup>26</sup> (3) and a life table for OCM risk estimation developed from the Prostate Cancer Outcomes Study (PCOS)<sup>10</sup> (Table 3.1). The CaPSURE nomogram and PCOS life tables were selected for evaluation as they represent two main approaches to risk estimation (nomograms and life tables) and could be reasonably evaluated with the limitations of the data available for this study. Two other available tools for OCM risk estimation were not evaluable either due to limitations in reproducing predictors or because the tool only became available as this dissertation was finalized (Table 3.1).

### **Data Source**

This study utilized the Surveillance, Epidemiology, and End Results (SEER) - Medicare Health Outcomes Survey (MHOS) linked database. The SEER-MHOS database provides data on 19,727 men with PCa with follow-up survival data available through February 2013. Patients' sociodemographic, tumor, and treatment characteristics are populated from the National Cancer Institute's SEER cancer registry. The SEER program collects comprehensive cancer data representative of 26% of the U.S. population through regional registries across the U.S.<sup>54</sup> Self-reported comorbidity and health behavior data were collected through the Centers for Medicare & Medicaid Services' (CMS) MHOS survey. Beginning in 1998 CMS annually surveyed Medicare managed care plan participants to monitor health outcomes, with response rates ranging from 64-72%.<sup>48</sup> Medicare managed care enrollees account for roughly 19% of all

Medicare beneficiaries. From 1998-2011 over 1.6 million enrollees completed surveys for the MHOS.<sup>55</sup> Details of the SEER-MHOS linkage and prospective data collection methods have been previously described.<sup>48</sup>

### **Study Population**

Patients were selected if newly diagnosed with PCa between January 1, 1998 and December 31, 2009, and if they completed an MHOS survey within the 3 years preceding their PCa diagnosis. Exclusion criteria included diagnosis of PCa on autopsy or death certificate or if diagnosed with regionalized or metastasized tumors (stage > cT3a). For the primary analysis the sample was restricted to patients age <80 at PCa diagnosis as the decision to undergo definitive treatment is most relevant in this population. Secondary analyses included all patients age 66 and older at PCa diagnosis in order to assess the performance of risk estimates in a population that included the oldest patients.

### **Data Collected**

Age, demographic, comorbidity, and treatment variables were selected to approximate variables from previously developed tools for OCM risk estimation.<sup>10,26</sup> Age at diagnosis was determined from the SEER registry. Comorbidity was assessed with two methods. A “CaPSURE comorbidity count” variable was generated utilizing a count of self-reported conditions in MHOS that overlap with disease categories used to generate the comorbidity count for the nomogram: hypertension, heart disease, stroke, diabetes, chronic obstructive pulmonary disease [COPD], cancer.<sup>26</sup> A Charlson Comorbidity Index (CCI) score was also generated utilizing Charlson weights for 8 self-reported conditions in MHOS (myocardial infarction, congestive heart failure, stroke, COPD, diabetes, inflammatory bowel disease, paralysis, other cancer), which overlap

with conditions in the CCI.<sup>34</sup> Full details on this study's adaptations to comorbidity inputs for the CaPSURE and PCOS tools are available in Supplement 3.A. Race, reported in SEER, was categorized as white, black, Hispanic, Asian/Pacific Islander, and other. SEER collects treatment information on patients' first course of therapy, or primary surgical and radiotherapies. We considered patients who underwent radical prostatectomy as having received definitive surgical therapy and classified patients undergoing brachytherapy, external beam radiation, or a combination of the two as having received definitive radiotherapy.

### **Survival and Mortality Outcomes**

Survival and detailed cause of death were ascertained through the SEER portion of the linked dataset. Patient deaths were classified as due to PCSM versus OCM using the SEER cause of death recode variable (codpub). Survival was calculated as the difference between the date of diagnosis and the date of death, or last SEER follow-up date for censored patients. Patients not experiencing OCM or PCSM within 10 years of PCa diagnosis were censored at 10 years if followed  $\geq 10$  years after diagnosis, or at time of last SEER follow-up if followed  $< 10$  years.

### **Assignment of OCM Risk Estimates**

Using the Social Security life tables annual risk of mortality, reported for the general male U.S. population,<sup>71</sup> the risk of dying within the next 10 years of all causes was computed and assigned to each patient with age rounded to integer values. OCM risk estimates were also derived for all patients in the database using the CaPSURE and PCOS tools. Inputs for the CaPSURE and PCOS tools were approximated closely, but were adapted as described below when limited by the available SEER-MHOS data.

The CaPSURE nomogram OCM risk scores were derived based on age, “CaPSURE comorbidity count,” radiotherapy or conservative management vs. radical prostatectomy, and race black vs. white or other.<sup>26</sup> Because data on androgen deprivation therapy were not available in SEER-MHOS, nomogram risk scores were computed without this input. While the CaPSURE tool was originally developed with data from definitively treated patients, the developers have recommended the nomogram for pretreatment OCM risk estimation in allcomers.<sup>26</sup> Thus, risk scores were also generated for conservatively managed patients. Conservatively managed patients were assigned the same points as radiotherapy treated patients, as conservatively managed patients have a higher risk of OCM than radical prostatectomy treated patients (as demonstrated in Chapter II), and this was thought to mirror how a clinician may apply the risk calculator to patients in a pre-treatment clinical setting. PCOS life table risk scores were assigned to patients based on comorbidity count from approximated CCI scores and patients’ age at diagnosis.<sup>10</sup> Supplement 3.A describes differences between original CaPSURE and PCOS model comorbidity inputs and adaptations made to model inputs in more extensive detail.

### **Statistical Analysis**

Predictive accuracy was evaluated by dividing the population into predicted risk groups and assessing the prevalence of observed mortality within each risk group. Risk scores were derived from each prediction method and divided into quintiles. Patients were assigned to quintiles of risk, defined separately for each tool. Kaplan-Meier methods were used to estimate observed all-cause mortality for patients in each quintile of Social Security predicted mortality risk. To estimate observed OCM in the study population, cumulative incidence of 10-year OCM was computed utilizing modified



Kaplan-Meier methods that account for the competing risk of dying of PCa.<sup>64</sup> Observed cumulative incidence of OCM was compared to predicted risk for each of the risk estimation methods at each risk quintile. The percentage of subjects assigned a risk score  $>0.5$  was noted for each method as this threshold is thought to correspond to a life-expectancy  $<10$  years.<sup>12</sup> The sensitivity, specificity, positive and negative predictive values of having  $>50\%$  predicted risk were calculated for each method. The “gold-standard” comparison for these assessments was death or survival during 10 years of follow-up after PCa diagnosis.

Discrimination with survival data was measured with Harrell’s c-index (concordance-index).<sup>64</sup> This index evaluates whether pairs of patients in the dataset have the relative outcome that would be expected given the risk score assigned from the model. A pair is considered concordant if a patient with higher predicted risk experiences the event before a patient with a lower risk score. The pair is considered discordant if a patient with a lower risk score experiences the event sooner than someone with a higher risk score. The index evaluates all pairs of patients in the data where at least one individual experienced the event. The index is calculated as the ratio of evaluable concordant to discordant pairs with a range of 0.5 to 1.0. A model that performs no better than a random prediction will achieve a score of 0.5 while a model that perfectly discriminates between all comparable pairs of individuals in the data set is rated 1.0. C-index values  $>0.7$  are considered of modest clinical utility, while values  $>0.8$  are considered genuinely clinically useful; below these thresholds models are considered of limited to poor clinical value.<sup>72,73</sup>

To evaluate whether predictors reported in the CaPSURE OCM risk estimation nomogram remained associated with OCM in SEER-MHOS data and had similar sized

effects on mortality risk, Fine and Gray competing risks regression for OCM risk was fitted with the re-approximated predictors from the nomogram, with PCa death as the competing risk.<sup>74</sup> This analysis was not performed for the PCOS tool predictors as the original publication did not report details of the regression model results, limiting the ability to make comparisons.<sup>10</sup> The complete case method was used. The cumulative incidence analyses of OCM were conducted with SAS v9.3 (SAS Institute, Cary, NC), while all other analyses utilized Stata IC 12 software (College Station, TX).

## RESULTS

Of the 19,727 patients with PCa linked between SEER and MHOS databases, 2,931 were newly diagnosed with localized, clinical stage T1a-T3a PCa between January 1, 1998 and December 31, 2009 and completed an MHOS survey within 3 years preceding their PCa diagnosis. The primary analysis included 2,425 patients age 80 or younger at PCa diagnosis. Median follow-up was 7.7 years, over which 24.3% of eligible men died of OCM and 3.7% of PCa. Complete sample characteristics for the primary analysis cohort are reported in Table 3.2.

### **Social Security All-Cause Mortality Predictions**

The Social Security risk tables over-predicted all-cause mortality in the study population (Table 3.3). Using the Social Security tables, patients in the lowest risk quintile had a predicted 26% all-cause mortality rate, while the observed all-cause mortality rate in the SEER-MHOS population was 20% (95% CI 17-25%). Similarly, patients in the highest risk quintile had a predicted 58% all-cause mortality rate, but an observed rate of only 42% (95% CI: 37-48%) mortality as estimated with Kaplan-Meier methods. Harrell's c-index was 0.59 for the Social Security all-cause mortality

predictions, suggesting poor discrimination between individuals who died or survived over 10 years of follow-up. In contrast to all-cause mortality, OCM rates were consistently 3-7% lower across all quintiles of predicted risk. This difference may be due to the low additional risk of PCSM that may be captured in the all-cause mortality risk estimate but is not accounted for when estimating only OCM risk (Table 3.3).

Overall, 25% of the sample received a Social Security life table risk score of 50% or higher, suggestive of a <10 year life expectancy. This >50% threshold resulted in a 35% sensitivity for all-cause mortality observed during the available follow-up in the SEER-MHOS population; the positive predictive value of the life tables compared to observed deaths was 31%, and the negative predictive value was 81% (Table 3.3).

### **Other Cause Mortality Prediction Tools**

Tools specifically developed to measure OCM more often provided accurate estimates of OCM rates. However, both the CaPSURE nomogram and PCOS life table OCM risk estimation tools still somewhat over predicted risk compared to the observed OCM rates obtained from the SEER-MHOS cohort (Table 3.3). For patients in the lowest CaPSURE and PCOS risk quintiles the tools predicted average OCM risk from 14-22% while the OCM rate for patients in these lowest risk quintiles was only 14-15%. For patients in the highest CaPSURE and PCOS risk quintiles the tools predicted 46-57% OCM risk; in comparison, the rate of OCM in the highest quintile groups only ranged from 38-39%. Overall, the PCOS life table predictions were closest to observed OCM rates across the greatest number of risk groups in the SEER-MHOS study population, with well-calibrated estimates for quintile 1 and 4, but slightly overestimated OCM in the other quintiles (Table 3.3). For the highest risk quintile of patients, the CaPSURE nomogram provided the most accurate predictions. Both the CaPSURE nomogram and

PCOS life tables improved upon Social Security estimates in terms of discriminating between those who died and those who did not. Risk estimates from both prediction tools achieved a Harrell's c-index of 0.64.

Utilizing a 50% OCM risk threshold for determining <10 year life expectancy was insufficient as a potential threshold for clinical action; positive predictive value for OCM was highest at 37% for the CaPSURE nomogram, and lowest for the PCOS life tables at 30%. Sensitivity for OCM was poor for both methods; the CaPSURE nomogram had a sensitivity of 8% with a specificity of 97% while the PCOS life tables were only marginally better with a 13% sensitivity and 93% specificity.

#### **Secondary Analyses: Predictions for Older Patients 66+**

There were 2,854 patients age 66 and older included in the secondary analyses. Population characteristics for the secondary analysis cohort are detailed in Table 3.4. The performance of the OCM estimation tools generally improved in the older population.

Social Security life tables continued to overestimate all-cause mortality in this population across all risk quintiles (Table 3.5). The lowest risk quintile of patients had a predicted 29% all-cause mortality rate, while observed all-cause mortality was 19% (95% CI: 16-22%), and patients in the highest risk quintile had an average 77% predicted all-cause mortality rate, but only experienced 59% (95% CI: 53-65%) mortality as estimated with Kaplan-Meier methods. The risk of dying of all-causes vs. OCM diverged even more in this older cohort (Table 3.5). Harrell's c-index improved to 0.66 for the Social Security all-cause mortality predictions, suggesting improved discrimination among older patients. A risk score of 50% or higher, suggestive of a <10 year life expectancy, was assigned to 39% of the population. This threshold provided 56% sensitivity for all-cause deaths

observed during the available follow-up, had a positive predictive value of 39%, and negative predictive value of 81% (Table 3.5).

The CaPSURE and PCOS OCM prediction tools also continued to over predict OCM risk, although the extent to which overestimation occurred diminished (Table 3.5). In this cohort of older men, the CaPSURE nomogram had markedly improved performance among the highest OCM risk group where the model and observed estimates were very similar (60% predicted vs. 58% observed). PCOS life table estimates overlapped with observed OCM rates for more quintiles (1, 3 and 4) and the degree of overestimation diminished for quintile 5. Discrimination (c-index) improved for the two tools ranging from 0.65-0.68 (Table 3.5). A risk score of 50% continued to be a poor threshold for OCM prediction, with sensitivity ranging from 15-27%. Table 3.5 details full performance of this threshold.

#### **Re-estimation of CaPSURE model coefficients**

For the CaPSURE nomogram, refitting of a Fine and Gray competing risks regression model in the primary analysis cohort (patients <80 years of age at diagnosis) revealed very similar associations between the key predictors (age and comorbidity count) and the risk of OCM (Table 3.6). Radiotherapy treatment vs. radical prostatectomy was associated with a greater likelihood of OCM in this cohort (HR: 1.64, 95% CI: 1.08-2.46 vs. previously reported HR: 1.26, 95% CI 1.07-1.49). However, African American race was no longer significantly associated with OCM in this cohort.

#### **DISCUSSION**

This study presents an evaluation of currently available methods for estimating OCM risk in a cohort of older American men with localized PCa. The objective of this

work was to determine the performance of Social Security life table mortality risk estimates, recommended for life expectancy estimation, as compared to available OCM risk estimation methods. Accurate and reliable prediction of life expectancy, which is primarily defined by OCM risk, is a necessary prerequisite for improving treatment decision-making for PCa and reducing overtreatment.<sup>12,14,15</sup> As applied to this data source, the mortality estimates derived from the Social Security life tables overestimated all-cause mortality and OCM risk and performed poorly in discriminating between individuals who survived and died, well below thresholds for making reliable clinical distinctions at the individual patient level.<sup>72</sup> OCM risk estimation tools derived using data from CaPSURE and PCOS improved upon Social Security estimates, with less overestimation of OCM risk and better discrimination between those who died and those who did not. However, overall discrimination of both CaPSURE and PCOS OCM risk estimation tools remained limited with c-index values of 0.64 among patients less than 80 years of age at diagnosis, suggesting these tools may have suboptimal performance for individualized clinical decision-making. Future OCM risk estimation tools may benefit from incorporation of additional predictors which help to more accurately discriminate between higher and lower risk patients.

The Social Security life tables, which past guidelines have recommended clinicians rely upon for determining life expectancy<sup>7</sup> and which rely only on age to derive predictions, appear to provide the poorest risk classification of patients among available methods as well as some of the least accurate predictions of all-cause and true OCM risk in this cohort of older Americans. The PCOS life tables and CaPSURE nomogram, which additionally account for self-reported comorbidity, improved upon the performance of the Social Security life table estimates and provided the most optimal balance of

better estimating the true rate of OCM as well as discriminating between individuals who survived and died. However, further improvements to all of the models assessed may be required before they can be reliably applied to individual patients in the clinic.

Ultimately, these tools are intended to aid in making better treatment decisions, which requires defining thresholds for changing clinical action. If these three tools were relied upon for making clinical treatment decisions, utilizing a recommended cut point of 50% OCM risk to predict <10 years life expectancy,<sup>12</sup> depending on which tool was utilized, a substantially different proportion of patients would be recommended for conservative treatment. Social Security life tables would result in almost 25% to 39% of patients being conservatively managed while other methods would lead to just fewer than 4% being conservatively managed. This crude cut point-based approach for decision-making may not be an optimal mechanism for utilizing these risk estimation tools. The 50% threshold resulted in poor sensitivity for detecting deaths. While the CaPSURE nomogram and PCOS risk tables provided the best estimates of the true rate of OCM, utilizing a threshold of 50% risk as a predictor of <10 year life expectancy only detected 4% to 8% of the observed deaths. The vast majority of the observed OCM deaths occurred among patients with a <50% predicted risk of OCM. Perhaps a more useful way to utilize such tools would be to more carefully consider conservative management among the highest 2 or 3 risk quintiles of patients who account for the majority of the observed OCM deaths during follow-up.

Re-estimation of the CaPSURE nomogram regression model in the SEER-MHOS population revealed that the associations for age and comorbidity- the two most important predictors in the model- were closely reproduced. This may suggest that some of the differences observed in OCM risk across populations may be attributable to

differences in the baseline risk of OCM. Thus, providing clinicians with mechanisms for recalibrating risk estimates to better fit mortality rates in their populations may be one solution to improving the accuracy of these tools. The differences in risk estimates may also be attributable to the varied prevalence of comorbidities between the cohorts in addition to unmeasured confounding.

This study has several limitations. While this work provides important insights into the performance of available mortality risk estimation tools, poor performance of any particular tool may partly be attributed to limitations in approximating model inputs. While efforts were made to approximate comorbidity assessments from the published tools, modifications were required as described in Supplement 3.A. The approach presented here should still be informative to clinicians who may similarly attempt to approximate model inputs in a real-world setting, and may provide a cautionary example highlighting the importance of reproducing model inputs as closely as possible. It should also be noted that life tables required assigning the same risk scores to large groups of patients, limiting the opportunity for the PCOS tool to discriminate between individuals' risk. Were a continuous PCOS prediction model available, discrimination would likely be improved over what is reported in this manuscript using life table OCM risk estimates. There is additionally some potential for misclassification of death, the outcome variable. However, prior work has shown the SEER mechanism for accounting for and attributing cause-specific death to be reliable and valid.<sup>75</sup>

Future OCM risk estimation tools should consider incorporating easily obtainable, well-defined predictors that clinicians can easily reproduce to improve the discrimination between individuals who die of OCM and those who do not. The addition of comorbidity to age improved discrimination, as evidenced by all tools providing



improved risk classification over Social Security life table risk estimates. At best, the current models have limited predictive value in terms of classifying patients from highest to lowest risk. Prior work has suggested that patient-reported measures of functioning as well as sociodemographic variables may have value in predicting OCM.<sup>33</sup> Improving risk classification of prediction tools via parsimonious addition of high value predictors could add to their clinical utility. Additionally, incorporation of treatment variables complicates application of OCM risk estimation tools as a pre-treatment decision aid, as was highlighted when applying the CaPSURE nomogram risk estimates to this population. Limiting risk estimation tools to pre-treatment variables would also promote their utility in decision-making. Finally, the accuracy of the estimates from each of the tools was limited in the SEER-MHOS population, likely because the death rates in the SEER-MHOS database were relatively low. Thus providing a mechanism for clinicians to recalibrate risk estimation tools to death rates observed in their populations would also assist in promoting the accuracy of estimates from these tools.

## **CONCLUSIONS**

The evaluated OCM risk estimation tools provide more accurate classification of patient mortality risk and absolute estimates of this risk than Social Security life tables. However, the tools remain limited in their ability to distinguish between individuals likely to die of OCM versus those who will not, which may limit the clinical utility of these tools.

**Table 3.1: Published other cause mortality risk estimation tools assessed in Chapter III vs. recommended Social Security life table mortality estimates**

|  | Publication First Author                     | Database Utilized             | Type of Risk Estimation Tool              | Outcome Estimated           | Predictors   |
|--|--|-------------------------------|---|-----------------------------|--|
| Assessed in Current Study                  | Social Security Administration <sup>71</sup> | U.S. General Population Males | Life table (categories from table matrix) | 10-year all-cause mortality | <ul style="list-style-type: none"> <li>• Age at diagnosis</li> </ul>   |
|  | Kutikov <sup>26</sup>                        | CaPSURE                       | Nomogram (continuous predictions of risk) | 10-year OCM                 | <ul style="list-style-type: none"> <li>• Age at diagnosis</li> <li>• Comorbidity count</li> <li>• Treatment with radiotherapy vs. radical prostatectomy</li> <li>• Receipt of androgen deprivation therapy*</li> <li>• Race (black vs. white)</li> </ul> |
|  | Daskivich <sup>10</sup>                      | PCOS                          | Life table (categories from table matrix) | 10-year OCM                 | <ul style="list-style-type: none"> <li>• Age at diagnosis</li> <li>• Self-reported list of comorbid conditions (Supplement 3.A)</li> </ul>   |
| Not Assessed In Current Study <sup>‡</sup> | Daskivich <sup>12</sup>                      | SEER-Medicare                 | Life table (categories from table matrix) | 10-year OCM                 | <ul style="list-style-type: none"> <li>• Age at diagnosis</li> <li>• Claims-based Charlson Comorbidity Index</li> </ul>  |
|  | Hoffman <sup>27</sup>                        | PCOS                          | Nomogram (continuous predictions of risk) | 10-year OCM                 | <ul style="list-style-type: none"> <li>• Age at diagnosis</li> <li>• Race /Ethnicity (Hispanic vs. white vs. black)</li> <li>• Self-rated health (excellent/very good/good/fair-poor)</li> </ul>   |

\*Predictor unavailable in SEER-Medicare database but has minor contribution to overall risk score

‡ After consultation with Dr. Daskivich et al., the SEER-Medicare life table estimates were not assessed in the current study as the claims-based specification of comorbidity could not be replicated well in the SEER-MHOS database. The Hoffman nomogram was published after the analyses and writing for Chapter III were complete and thus was not available for assessment during the course of this study. Its performance was instead briefly evaluated in Chapter IV of this dissertation. The Walz and Tewari nomograms for all-cause mortality prediction (listed in Table 1.1) were not evaluated in this study as they do not provide specific assessments of OCM risk which the field has moved toward for more accurate distinct estimates of OCM.

**Table 3.2: Patient characteristics: primary analysis sample**

|   | <b>Total</b> | <b>Prostate-Specific<br/>Death</b> | <b>Other Cause<br/>Mortality</b> | <b>Surviving</b> |
|---|--------------|------------------------------------|----------------------------------|------------------|
| <b>No. of patients (%)</b>                  | 2425         | 76 (3)                             | 465 (19)                         | 1884 (78)        |
| <b>Mean age at diagnosis</b>                | 72.9         | 74.5                               | 73.8                             | 72.6             |
| <b>Race/ethnicity (%)</b>                   |              |                                    |                                  |                  |
| White                                       | 1879 (77)    | 57 (75)                            | 371 (80)                         | 1451 (77)        |
| Black                                       | 290 (12)     | ~                                  | 55 (12)                          | 223 (12)         |
| Hispanic/Asian/Pacific Islander or other    | 256 (11)     | ~                                  | 39 (8)                           | 210 (11)         |
| <b>CaPSURE Comorbidity Count (%)</b>        |              |                                    |                                  |                  |
| 0   | 476 (36)     | 16 (21)                            | 81 (17)                          | 516 (27)         |
| 1   | 422 (32)     | 14 (18)                            | 130 (28)                         | 642 (34)         |
| ≥2  | 418 (31)     | 46 (60)                            | 254 (54)                         | 726 (39)         |
| <b>Charlson Comorbidity Index Score (%)</b> |              |                                    |                                  |                  |
| 0   | 1326 (54)    | 31 (40)                            | 177 (38)                         | 1118 (59)        |
| 1   | 586 (24)     | 18 (24)                            | 130 (28)                         | 438 (23)         |
| ≥2  | 513 (21)     | 27 (35)                            | 158 (34)                         | 328 (17)         |
| <b>PCa Management</b>                       |              |                                    |                                  |                  |
| Conservative                                | 794 (33)     | 46 (60)                            | 197 (42)                         | 551 (29)         |
| Radical Prostatectomy                       | 323 (13)     | ~                                  | 28 (6)                           | 294 (16)         |
| Radiation Therapy                           | 1308 (54)    | ~                                  | 240 (52)                         | 1039 (55)        |

~ exact n=, % not reportable per SEER-MHOS data use agreements as cell size <11 individuals for certain sub-categories

Further details on patient tumor characteristics for the identical sample can be found in Table 2.2 (Chapter II)

**Table 3.3: Comparison of predicted to observed percent deaths for three risk estimation methods: Social Security life tables, CaPSURE and PCOS tools in men age  $\leq 80$**

| Risk Estimation Tool       | Risk Type                                 | Percent 10-year Mortality by Quintile <sup>Δ</sup> of Risk (95% CI) |            |            |                   |            | Harrell's c-index | Performance Measures                                     |
|----------------------------|---|---|------------|------------|-------------------|------------|-------------------|--|
|                            |   | Quintile 1  | Quintile 2 | Quintile 3 | Quintile 4        | Quintile 5 |                   |  |
| Social Security Life Table | Predicted                                 | 26  | 33         | 40         | 49                | 58         | 0.59              | >50% risk: 25%<br>**PPV: 31% Se: 35%<br>NPV: 81% Sp: 78% |
|                            | Observed All-Cause Mortality <sup>α</sup> | 20 (17-25)  | 24 (20-29) | 25 (21-29) | 33 (28-39)        | 42 (37-48) |                   |  |
|                            | Observed OCM <sup>±</sup>                 | 18 (15-22)  | 20 (16-25) | 22 (18-26) | 29 (24-34)        | 35 (29-40) |                   |  |
| CaPSURE Nomogram           | Predicted                                 | 22  | 28         | 33         | 38                | 46         | 0.64              | >50% risk: 4%<br>PPV: 37% Se: 8%<br>NPV: 81% Sp: 97%     |
|                            | Observed OCM <sup>±</sup>                 | 14 (11-18)  | 21 (17-25) | 23 (18-29) | 30 (26-35)        | 39 (33-45) |                   |  |
| PCOS Life table            | Predicted                                 | <b>14</b>   | 35         | 40         | <b>42</b>         | 57         | 0.64              | >50% risk: 8%<br>PPV: 30% Se: 13%<br>NPV: 81% Sp: 93%    |
|                            | Observed OCM <sup>±</sup>                 | <b>15 (12-20)</b>   | 19 (17-22) | 31 (27-37) | <b>40 (31-48)</b> | 38 (30-46) |                   |  |

<sup>Δ</sup> Quintiles were separately defined for each tool, with patients assigned to different quintiles based on the predicted risk from each tool.

**Bold** font among numerical values indicates quintiles where 95% confidence intervals for cumulative incidence estimates for OCM (observed deaths) overlapped with the predicted OCM death rate

<sup>α</sup> Observed all-cause mortality rates were determined utilizing Kaplan-Meier methods for all-cause mortality

<sup>±</sup> Observed OCM rates were determined utilizing modified Kaplan-Meier methods for competing risks analysis (cumulative incidence distributions)

**>50% risk**= % of patients assigned higher than 50% risk score

**PPV**= positive predictive value

**NPV**=negative predictive value

**Se**= sensitivity

**Sp**= specificity

\*\*performance measures for Social Security life tables are calculated with all-cause mortality, not other cause mortality

Table 3.4: Patient characteristics: secondary analysis sample (age 66+ group)

|   | Total     | Prostate-Specific Death | Other Cause Mortality | Surviving |
|---|-----------|-------------------------|-----------------------|-----------|
| <b>No. of patients (%)</b>                  | 2854      | 116 (4)                 | 648 (23)              | 2090 (73) |
| <b>Mean age at diagnosis</b>                | 75.1      | 78.8                    | 77.3                  | 74.3      |
| <b>Race/ethnicity (%)</b>                   |           |                         |                       |           |
| White                                       | 2221 (78) | 90 (78)                 | 524 (81)              | 1607 (77) |
| Black                                       | 311 (11)  | 13 (11)                 | 66 (10)               | 232 (11)  |
| Hispanic/Asian/Pacific Islander or other    | 322 (11)  | 13 (11)                 | 58 (9)                | 251 (12)  |
| <b>CaPSURE Comorbidity Count (%)</b>        |           |                         |                       |           |
| 0   | 730 (26)  | 24 (21)                 | 118 (18)              | 588 (28)  |
| 1   | 937 (33)  | 24 (21)                 | 184 (28)              | 729 (35)  |
| ≥2  | 1187 (42) | 68 (58)                 | 346 (53)              | 773 (37)  |
| <b>Charlson Comorbidity Index Score (%)</b> |           |                         |                       |           |
| 0   | 1582 (55) | 50 (43)                 | 259 (40)              | 1273 (61) |
| 1   | 674 (24)  | 27 (23)                 | 172 (27)              | 475 (23)  |
| ≥2  | 598 (21)  | 39 (34)                 | 217 (33)              | 342 (16)  |
| <b>PCa Management</b>                       |           |                         |                       |           |
| Conservative                                | 1148 (40) | 83 (71)                 | 356 (54)              | 709 (34)  |
| Radical Prostatectomy                       | 300 (11)  | ~                       | 26 (4)                | 273 (13)  |
| Radiation Therapy                           | 1406 (49) | ~                       | 266 (41)              | 1108 (53) |

~ exact n=, % not reportable per SEER-MHOS data use agreements due to small cell size

Mean follow-up time for this cohort was 7.2 years

**Table 3.5: Comparison of predicted to observed percent deaths for three risk estimation methods: Social Security life tables, CaPSURE and PCOS tools in secondary analysis population (Age 66+)**

| Risk Estimation Tool       | Risk Type                                 | Percent 10-year Mortality by Quintile <sup>A</sup> of Risk (95% CI) |            |                   |                   |                   | Harrell's c-index | Performance Measures                                     |
|----------------------------|---|---|------------|-------------------|-------------------|-------------------|-------------------|--|
|                            |   | Quintile 1  | Quintile 2 | Quintile 3        | Quintile 4        | Quintile 5        |                   |  |
| Social Security Life Table | Predicted                                 | 29  | 37         | 45                | 56                | 77                | 0.66              | >50% risk: 39%<br>**PPV: 38% Se: 56%<br>NPV: 81% Sp: 67% |
|                            | Observed All-Cause Mortality <sup>α</sup> | 19 (16-22)  | 27 (23-30) | 30 (25-35)        | 39 (34-44)        | 59 (53-65)        |                   |  |
|                            | Observed OCM <sup>±</sup>                 | 17 (14-20)  | 23 (20-27) | 26 (21-31)        | 33 (28-37)        | 49 (44-55)        |                   |  |
| CaPSURE Nomogram           | Predicted                                 | 24  | 33         | 38                | 45                | <b>60</b>         | 0.68              | >50% risk: 13%<br>PPV: 46% Se: 27%<br>NPV: 81% Sp: 91%   |
|                            | Observed OCM <sup>±</sup>                 | 14 (11-17)  | 24 (21-28) | 24 (19-30)        | 36 (32-41)        | <b>58 (51-64)</b> |                   |  |
| PCOS Life table            | Predicted                                 | <b>14</b>   | 35         | <b>40</b>         | <b>42</b>         | 57                | 0.65              | >50% risk: 8%<br>PPV: 40% Se: 15%<br>NPV: 79% Sp: 93%    |
|                            | Observed OCM <sup>±</sup>                 | <b>15 (11-19)</b>   | 23 (21-26) | <b>36 (32-41)</b> | <b>44 (37-51)</b> | 46 (39-53)        |                   |  |

<sup>A</sup> Quintiles were separately defined for each tool, with patients assigned to different quintiles based on the predicted risk from each tool.

**Bold** font among numerical values indicates quintiles where 95% confidence intervals for cumulative incidence estimates for OCM (observed deaths) overlapped with the predicted OCM death rate

<sup>α</sup> Observed all-cause mortality rates were determined utilizing Kaplan-Meier methods for all-cause mortality

<sup>±</sup> Observed OCM rates were determined utilizing modified Kaplan-Meier methods for competing risks analysis (cumulative incidence distributions)

**>50% risk**= % of patients assigned higher than 50% risk score

**PPV**= positive predictive value

**NPV**=negative predictive value

**Se**= sensitivity

**Sp**= specificity

\*\*performance measures for Social Security life tables are calculated with all-cause mortality, not other cause mortality

**Table 3.6: Validation of the CaPSURE nomogram predictors for 10-year other cause mortality**

| Predictors                        | Original Model Estimates <sup>a</sup> |           |         | Validation: SEER-MHOS 10-year OCM Model Estimates |           |         |
|-----------------------------------|---------------------------------------|-----------|---------|---|-----------|---------|
|                                   | Hazard Ratio                          | 95% CI    | p-value | Hazard Ratio                                      | 95% CI    | p-value |
| <b>Age at diagnosis</b>           | 1.06                                  | 1.05-1.08 | <0.001  | 1.06  | 1.02-1.09 | <0.001  |
| <b>Number of comorbidities</b>    | 1.23                                  | 1.15-1.32 | 0.015   | 1.35  | 1.22-1.48 | <0.001  |
| <b>African American vs. white</b> | 1.34                                  | 1.03-1.73 | 0.03    | 0.88  | 0.59-1.32 | 0.545   |
| <b>RT vs. RP<sup>#</sup></b>      | 1.26                                  | 1.07-1.49 | 0.006   | 1.64  | 1.08-2.46 | 0.018   |

<sup>a</sup> Kutikov A, et al. (2012). Evaluating prostate cancer mortality and competing risks of death in patients with localized prostate cancer using a comprehensive nomogram. *Prostate Cancer and Prostatic Diseases*, 15(4), 374–9.

The analysis for the CaPSURE Model was based on a subset of 1629 complete cases who underwent either RT or RP. Conservatively managed cases were excluded as the original Kutikov/CaPSURE model was developed without conservatively managed patients.

### Supplement 3.A: Detailed methods utilized for approximating and modifying CaPSURE and PCOS risk estimation tool comorbidity assessments

**CaPSURE Nomogram:** The CaPSURE comorbidity count could be approximated with 6 of 7 conditions available. There was no information available in SEER-MHOS on self-reported renal disease and there were no alternative mechanisms for assessing renal disease, thus this condition was left out of the “CaPSURE comorbidity count approximation.” The table below summarizes the overlap between the original tool definitions and approximations in this study.

| CaPSURE Tool Original Comorbidities   | SEER-MHOS Conditions Available and Utilized for “CaPSURE Comorbidity Count” Approximation   |
|---|---|
| Hypertension<br>Heart disease<br><br>Stroke<br>Diabetes<br>Lung disease<br><br>Cancer<br><br>Kidney disease | Hypertension<br>Acute myocardial infarct, congestive heart failure, angina, coronary artery disease, other heart disease<br>Stroke, paralysis<br>Diabetes<br>Chronic obstructive pulmonary disease or emphysema<br>Other prior cancers or developed within 1 year of PCa diagnosis<br>Not available |

**PCOS Life Tables:** There was data available for 10 of 12 PCOS conditions utilized for the PCOS comorbidity count variable originally reported in the development manuscript for this tool. Data on bleeding gastrointestinal ulcers and cirrhosis were not available in SEER-MHOS. However, model performance estimates revealed that the OCM risk estimates generated utilizing a close approximation of the PCOS comorbidity count provided greater overestimation of patient mortality risk. Further, when the eight conditions available in SEER-MHOS which overlap with the Charlson Comorbidity Index (see table below) were substituted with Charlson weights in lieu of the PCOS comorbidity count approximation, the assigned predicted OCM rates were much closer to observed mortality in the SEER-MHOS population. Thus, the choice was made to utilize Charlson Index approximations for comorbidity assessments as described in the Methods section, as this optimized the PCOS life table performance in this population. The table below summarizes the differences between the methods.

| PCOS Tool Original Comorbidities  | SEER-MHOS Conditions Available  | Overlapping Charlson Index Conditions Utilized for Comorbidity Approximation in Final Analysis  |
|---|---|---|
| Diabetes<br>Chronic lung disease<br><br>Congestive heart failure<br>Stroke<br>Myocardial infarction<br>Inflammatory bowel disease<br>Angina/ chest pain<br>Arthritis<br>Hypertension<br>Depression or anxiety<br><br>Bleeding gastrointestinal ulcer<br>Cirrhosis | Diabetes<br>Chronic obstructive pulmonary disease or emphysema<br>Congestive heart failure<br>Stroke, paralysis<br>Acute myocardial infarction<br>Inflammatory bowel disease<br>Angina<br>available but high prevalence<br>available but high prevalence<br>available as SF-36 MCS but high prevalence with this definition<br>Not available<br>Not available | Diabetes<br>Chronic obstructive pulmonary disease<br>Congestive heart failure<br>Stroke<br>Myocardial infarction<br>Inflammatory bowel disease<br>N/A<br>N/A<br>N/A<br>N/A<br><br>Not available<br>Not available<br>Other cancer<br>Paralysis |



## CHAPTER IV: SELF-REPORTED DATA IMPROVE PRETREATMENT PREDICTIONS OF THE RISK OF DEATH FROM OTHER CAUSES IN PATIENTS WITH LOCALIZED PROSTATE CANCER

### ABSTRACT

**Background:** Accurate estimation of life expectancy is important for making appropriate treatment decisions for men with prostate cancer (PCa), the majority of whom will die of non-prostate causes. This study sought to develop an improved model for estimating 10-year other cause mortality (OCM) risk utilizing an efficient combination of self-reported data from men newly diagnosed with localized PCa.

**Methods:** 2,425 patients, age <80, newly diagnosed with clinical stage T1-T3a PCa from 1998-2009, were identified from the Surveillance Epidemiology and End Results - Medicare Health Outcomes Survey database. Fine and Gray competing risks models for 10-year OCM were fitted with PCa deaths as competing events. Candidate predictors included: age, sociodemographic characteristics, comorbid medical conditions, elements of the SF-36 Health Survey, and activities of daily living. Akaike's Information Criterion (AIC) and Harrell's c-index (range: 0.5-1.0) guided model selection, optimizing model fit and discrimination between individuals who live and who die. As a benchmark, model discrimination was compared to predictions from two currently available nomograms for estimating non-prostate mortality risk.

**Results:** Over a median follow-up of 7.7 years, 76 men died of PCa-specific causes and 465 died of other causes. The final competing risks model for 10-year OCM included age at diagnosis, self-report derived Charlson Comorbidity Index score, self-rated general health (excellent-good vs. fair vs. poor), smoking at diagnosis, and marital status (married vs. all other) as predictors. Discrimination between survivors and those dying of

OCM improved over available nomograms (c-index of 0.70 vs. 0.64/0.65). The five factor model performed as well as models that included more detailed assessments of self-reported physical health, and activities of daily living.

**Conclusions:** This limited set of five self-reported characteristics may aid in more accurately estimating OCM risk prior to treatment decision-making.

## BACKGROUND

Accurate assessment of life expectancy is critical to enabling evidence-based treatment decision-making for the over 220,000 men diagnosed with prostate cancer (PCa) in the U.S. annually.<sup>1</sup> Guidelines consistently recommend that clinicians assess patients' life expectancy in the treatment decision-making process and reserve definitive treatment of localized tumors for men with at least a 10-year life-expectancy.<sup>7,9,53</sup> These recommendations arise from documented risks of treatment-associated morbidity,<sup>9</sup> and randomized clinical trial evidence demonstrating a lack of treatment benefit for individuals with follow-up of less than 8-10 years.<sup>76</sup> For men with localized tumors the average risk of dying of PCa in the 10 years following diagnosis is less than 5%, regardless of treatment.<sup>10,11</sup> In contrast, the risk of dying of non-prostate causes can range from as little as 6% to over 90% depending on an individuals' age, health and social factors.<sup>10,12-15</sup> Enabling clinicians to accurately determine non-prostate mortality risk is of high importance, especially given that currently a quarter to half of patients are likely overtreated, dying of non-PCa causes within 10 years of diagnosis.<sup>12</sup>

Currently available prediction tools largely rely on age and comorbidity for assessing mortality risk.<sup>10,12,26,27</sup> As Chapter III of this dissertation demonstrated, existing prediction tools are limited in their ability to accurately discriminate between individual

patients who will survive 10 years and those who will die of other causes,<sup>69</sup> particularly among patients 65-80 years of age for whom life expectancy determinations may highly influence treatment decisions. These tools do not meet thresholds for reliably distinguishing between those likely to live and die in a clinical setting.<sup>72</sup> There is, however, mounting evidence that additional self-reported factors have value in predicting other cause mortality (OCM) beyond comorbidity and age alone.<sup>27,33</sup> This study sought to identify an optimal combination of self-reported data for pretreatment estimation of the risk of OCM in men newly diagnosed with localized PCa.

## **METHODS**

### **Data Source**

This study utilized the Surveillance, Epidemiology, and End Results (SEER) - Medicare Health Outcomes Survey (MHOS) linked database which provides data on 19,727 men diagnosed with PCa through 2009. Follow-up survival data are available through February 2013. The National Cancer Institute's SEER cancer registry collects sociodemographic, tumor, and treatment data representative of 26% of the U.S. population.<sup>54</sup> The Centers for Medicare & Medicaid Services' (CMS) conducts the MHOS survey, annually collecting self-reported comorbidity and health behavior data from a sample of Medicare managed care plan participants across all of its plan offerings to monitor health outcomes with response rates of 64-72%.<sup>48</sup> Medicare managed care participants represent roughly 19% of all Medicare beneficiaries. The complete details of the SEER-MHOS linkage and data collection methods have been previously described.<sup>48</sup>

### **Study Population**

Patients were selected if <80 years of age when newly diagnosed with PCa between January 1, 1998 and December 31, 2009, having completed an MHOS survey within the 3 years before their PCa diagnosis. Exclusion criteria included diagnosis of PCa on autopsy or death certificate or regionalized or metastasized tumors (stage > cT3a).

### **Data Collected**

Age at diagnosis was determined from the SEER registry. Self-reported comorbidity data was available for the following conditions: hypertension; angina or coronary artery disease; myocardial infarction; other heart conditions; stroke; emphysema, asthma or chronic obstructive pulmonary disease (COPD); Crohn's disease, ulcerative colitis, or inflammatory bowel disease; arthritis of the hip or knee; arthritis of the hand or wrist; sciatica; diabetes; any cancer other than skin cancer; paralysis or weakness on one side of the body. An approximated Charlson Comorbidity Index (CCI) score was generated utilizing Charlson weights for 8 self-reported conditions in MHOS (myocardial infarction, congestive heart failure, stroke, COPD, diabetes, inflammatory bowel disease, paralysis, other cancer), which overlap with conditions in the CCI.<sup>34</sup> A crude count of available comorbid conditions was also assembled with conditions overlapping with prior OCM prediction tools.<sup>26</sup>

Self-reported physical and mental health were measured with the SF-36 Health Survey (v1)<sup>42,43</sup> which MHOS administered to participants before 2006 and the VR-12 Health Survey,<sup>58</sup> a shorter instrument with slight modifications, for men surveyed in 2006 and after. From the surveys, a Physical Component Summary (PCS) score, which summarizes patients' physical functioning, role limitations due to physical health, bodily pain and general health perceptions and a Mental Component Summary (MCS) score,

that summarizes patients' vitality, social functioning, role limitations due to emotional health, and mental health, were generated. PCS and MCS were scored by MHOS with an algorithm that allows for comparing scores across different survey forms.<sup>59</sup> Scores are normalized to a mean of 50 points in the general U.S. population with a standard deviation of 10 points, with higher scores representing better health.<sup>42,60</sup> Additionally a single item, available in both surveys, assessing self-rated general health as excellent, very good, good, fair, or poor was utilized.

MHOS also collected data on a number of self-reported activities of daily living. A prior MHOS report provided a scoring mechanism for a combination of 16 activities of daily living (ADL) and physical functioning (PF) items from the SF-36 Health Survey for the purposes of mortality prediction and case-mix adjustment, named the PF-ADL scale.<sup>77</sup> This study modified the PF-ADL scoring to utilize only 8 items available across all MHOS survey forms (moderate activities physical functioning item and ADLs: climbing stairs, bathing, dressing, eating, getting out of a chair, walking, toileting). Scores are reported on a 0-100 point scale, with higher scores representing better health.

Self-reported current smoking status (every day or some days) was determined from MHOS. Individuals who had unknown smoking status were categorized as non-smokers, as exploratory analyses revealed they experienced survival similar to non-smokers. Education was categorized as "more than a high school education" or "high school education or less" to provide consistency with prior definitions.<sup>33</sup> Race-ethnicity, reported in SEER, was categorized as white, black, Hispanic, Asian/Pacific Islander, and other. MHOS variables for self-reported data on marital status (married vs. all other), home ownership, and household income were also utilized.

### **Survival and Mortality Outcomes**

Survival and detailed cause of death were determined through the SEER portion of the dataset. Patients not experiencing death within 10 years of PCa diagnosis were censored at 10 years if followed  $\geq 10$  years after diagnosis, or at time of last SEER follow-up if followed  $< 10$  years. Patients who died were classified as having died of prostate-specific (PCSM) versus other causes; specific causes of OCM were confirmed using the SEER cause of death recode variable (codpub). Survival was calculated as the difference between the date of diagnosis and the date of death, or last SEER follow-up date for censored patients.

### **Statistical Analysis**

Patient characteristics were compared among those dying of PCSM, OCM and survivors using one-way analysis of variance tests and chi-squared tests as appropriate. Overall cumulative incidence of 10-year OCM was computed utilizing modified Kaplan-Meier methods that account for the competing risk of dying of PCSM. Fine and Gray competing risks models for 10-year OCM were fitted with self-reported pretreatment patient characteristics and with PCSM as the competing event.<sup>74</sup> Akaike's Information Criterion (AIC) and Harrell's c-index were utilized to guide model selection to optimize model parsimony and discrimination between individuals who survived and died over the 10 year follow-up period.<sup>65</sup> Minimizing AIC helps to reduce information loss and accounts for the tradeoff between goodness-of-fit and model complexity, penalizing more complex models that do not substantially fit the data better. Harrell's c-index (concordance index) assesses a model's ability to discriminate between individuals who survive and die. The c-index measures whether pairs of patients with different risk profiles have expected relative outcomes; a pair is concordant if a person with lower predicted risk has not

experienced the event by the time a person with higher predicted risk has the event; a pair is discordant if the person with lower risk experienced the event sooner. A pair is not evaluable unless at least one in the pair experiences the event. The c-index is the number of concordant pairs divided by the number of concordant plus discordant pairs. Models that are no better than a flip of a coin in assigning risk and distinguishing between surviving and dying patients will have a c-index of 0.5; models that perfectly classify all patients' risk from highest to lowest risk in the data set will receive a value of 1.0.

Candidate predictors of non-prostate mortality included age at diagnosis, comorbid medical conditions (a comorbidity count or as the approximated CCI), PCS, MCS, PF-ADL, self-rated general health, and sociodemographic variables (race, marital status, education level, household income).<sup>10,26,27,33,77</sup> Interaction terms between age and comorbidity, comorbidity and general health, age and general health, and smoking and comorbidity were considered in the modeling process to evaluate potential effect modification.<sup>29</sup> Risk scores were then generated from the final model utilizing the equation: cumulative risk of 10 year OCM =  $1 - (\text{baseline survival at 10 years})^{e^{(\sum x\beta)}}$ .

SEER-MHOS death rates are lower than observed in most populations which may lead to systematic underestimation of mortality risk in other populations.<sup>12</sup> To improve the generalizability of the final model risk estimates, the model was re-calibrated to an expected 10-year mortality rate of 36.9%, obtained by applying the Social Security life table age-matched 10-year all-cause mortality risk estimates (39.9%) in this population minus the roughly 3% prostate-specific mortality.<sup>71</sup> Recalibration was achieved by reducing the baseline survival rate in the risk equation presented above, to achieve an overall predicted 36.9% death rate for the whole population.

As a performance benchmark, discrimination of the new model was compared to the discrimination of two currently available nomograms for predicting OCM risk (Table 1.1).<sup>26,27</sup> The first benchmark nomogram, developed in the CaPSURE database, was modified slightly for use in the SEER-MHOS data and utilized age, comorbidity count, radiotherapy or conservative management vs. radical prostatectomy, and race black vs. white for generating OCM predictions.<sup>26</sup> Details of model adaptations are described in the methods of Chapter III of this dissertation. The other benchmark nomogram, developed by Hoffman et al. in the PCOS database, utilized age, race (categorized as Hispanic vs. non-Hispanic whites vs. black), and self-rated general health (excellent/very good/good/fair-poor) categorizations to predict OCM risk.<sup>27</sup> Risk scores from each model were assigned to all eligible patients in the SEER-MHOS database with complete data and c-index values were calculated for each model. Neither nomogram's c-index was reported in the original publications.<sup>26,27</sup>

As a sensitivity analysis, the model performance was also evaluated in a sample of SEER-MHOS patients who were over age 66 at diagnosis, including patients over age 80 who were excluded from the main analysis. Subject characteristics and methods for this sensitivity analysis are described in supplementary appendix 4.A.

## **RESULTS**

### **Patient demographics**

Mean patient age at diagnosis was 73 years. The majority of men (54%) had CCI scores of 0, ranging from 0-7 points, with 21% of the sample having scores of 2 or higher. Compared to surviving men, those who died of OCM were older, with higher comorbidity burden, worse PCS scores, worse general health, more likely to be smokers



at diagnosis and less often married. Full sample characteristics are summarized in Table 4.1.

### **Fine and Gray competing risks regression analysis**

Over a median follow-up of 7.7 years, 3.7% of the cohort died of PCa-specific causes and 24.3% of OCM. Median follow-up for survivors was 8.9 years (interquartile range 5.5-11 years). The combination of self-reported pretreatment factors with highest predictive value for death from other causes included age at diagnosis, self-reported CCI, self-rated general health (excellent to good vs. fair or poor), smoking at time of diagnosis, and marital status (married vs. all other) (Table 4.2). This model achieved a c-index of 0.70 vs. 0.64 and 0.65 for estimates from the currently available comorbidity and self-rated health based nomograms, respectively.

The five factors of age, CCI score, general health, smoking at diagnosis, and marital status performed as well as models that included more robust assessments of self-reported physical and mental health (PCS and MCS) and models that included activities of daily living (PF-ADL) (c-index was 0.70 for all tested variants with minimal differences in AIC). Other socioeconomic and race factors (education level, household income, homeownership) did not have significant associations with OCM when added to models that included age and CCI score, with the exception of being in the “other” race category, which did not have a clinically interpretable definition and represented a very small percentage (4%) of patients in the sample. The models discriminated better between surviving and dying individuals when comorbidity was assessed with a CCI score approximation than with a crude comorbidity count. No significant interactions were observed, with the exception of poor general health and a CCI score of 7, which

applied to <11 individuals in the entire sample, and was left out of the final model, having limited applicability.

### **Risk scores**

Table 4.3 demonstrates the range of obtained risk scores from the regression equation. Median predicted 10-year OCM risk was 20% (interquartile range 15-29%). Mortality risk estimates are also provided in a re-calibrated version for a higher expected death rate, obtained from the Social Security life tables (see Methods). This re-calibration provides a simulation of how risk estimates may have varied if the model were fitted in a population that experienced a higher death rate. When the estimates were re-calibrated, the median predicted 10-year OCM risk rose to 33% (interquartile range 25-44%).

Table 4.4 demonstrates predictions for five clinical scenarios, where the example patients have sequentially poorer health and are higher risk in each example. The examples demonstrate a much wider mortality risk spread than found in our data, which could be obtained if the model were utilized in a population with greater comorbidity burden, poorer health behaviors, and worse general health. In Table 4.4, estimates from the primary analysis in this study are listed as “low range” risk estimates, while estimates from the re-calibrated model are listed as the “high range” risk estimates.

### **Sensitivity analysis**

The model discrimination improved slightly when patients over 80 were added (c-index: 0.72), and continued to outperform previous prediction models which achieved c-index values of 0.68 and 0.69 in the population including patients >80 (supplement 4.A). The effects of individual predictors remained largely the same when the model was

refitted in this older population, indicating that the model should apply to older patients as well.

## DISCUSSION

This study developed a prognostic model for 10-year OCM risk, identifying a set of five pretreatment self-reported patient characteristics for mortality prediction, which performed as well as more detailed and burdensome evaluations of health. While accurately predicting OCM risk for an individual patient remains challenging, this model better discriminated between individuals dying and surviving, as compared to currently available risk estimation tools. Model estimates were also re-calibrated to age-matched general U.S. population death rates to improve the generalizability of predictions from this study. By relying on self-reported pre-treatment data (age, comorbidities, rating of general health, smoking, marital status), this study provides a simple, reproducible method for OCM risk estimation that may aid in facilitating shared decision making surrounding appropriately aggressive therapy for PCa.

There are a number of existing tools available for estimating the risk of dying of other causes.<sup>10,12,26,27,78</sup> Despite the availability of these tools there has been very limited adoption of these risk calculators and life tables in clinical practice; less than a quarter of PCa specialists utilize such tools.<sup>16</sup> Several factors limit the utility of existing tools and the likelihood of clinical uptake. As demonstrated in Chapter III of this dissertation, the estimated risk of OCM can vary widely depending on which tool is utilized and models have limited to poor discrimination between individuals likely to die of OCM and those likely to survive 10 years.<sup>69</sup> The variability in risk estimates may be due to differences in death rates in the populations that these tools were developed in and due to differences

in the specification of model inputs. For example, self-reported vs. claims-based assessments of comorbidity can yield widely different estimates of the prevalence of a particular condition, affecting the estimated risk score. Further, the thresholds at which conservative management strategies should be adopted are poorly defined. This complicates the interpretability of a particular percentage of estimated OCM risk and limits the clinical utility of these tools. Finally, existing tools are in the form of life tables or nomograms which are less user-friendly than online electronic interfaces. This study sought to address these key limitations. The final risk model developed in this dissertation is currently being adapted as an online risk calculation tool.

The final model risk factors selected in this study: age, comorbidity, self-reported health, marital status, and smoking, have all been shown to be important predictors of mortality and life-expectancy.<sup>10,12,26,27,33,77,78</sup> This model is the first to combine these factors in a prognostic calculator for 10-year OCM risk. Risk factors were obtained from self-report, which can be easily reproduced in any clinical setting.

Further, Chapter III of this dissertation demonstrated that SEER-MHOS death rates are among the lowest of all available cohorts of patients.<sup>10,12,26</sup> This would lead to underestimation of mortality risk should this model be applied to higher risk patient populations. To address this limitation, risk estimates were re-calibrated for higher expected death rate from the general U.S. male population Social Security estimates. All risk scores are presented with a low range and a high range estimate to reflect the potential variability in estimated risk across populations.

Risk scores can be interpreted based on the percentile that the risk score falls in relative to risk estimates from this population-based study (provided in Table 4.3). Selection of appropriately aggressive therapy may be achieved by more thoroughly

discussing the risks and benefits of definitive therapies, and conservative management alternatives, with patients in the highest risk categories (who may be expected to die within 10 years of diagnosis). For example, a 75 year-old, married, non-smoker, who rates his health as “good” and has one Charlson comorbidity point would be expected to have a 20% to 32% 10-year OCM risk which places him in the middle 50% of OCM risk among patients in the SEER-MHOS data. In this case, the risk score is inconclusive, and does not clearly promote a particular management strategy. In contrast, a 70 year old, married, smoker, with one Charlson comorbidity point and a self-rating of health as “fair” has a higher 38 to 56% predicted 10-year OCM risk, and falls in the highest 75% risk group of all patients (Table 4.3). More careful consideration of conservative management alternatives with such a patient may promote selection of appropriately aggressive therapy. To promote ease of use, an electronic risk calculation interface is provided to accompany this manuscript and ease the burden of risk estimation.

While more detailed assessments of health impairment were considered in the modeling process these variables did not improve upon the five factor models’ predictions in terms of discriminating between those who survived and died. Other factors considered included self-rated physical and mental health, measured as PCS and MCS scores, activities of daily living, and a more extensive comorbidity count. As these more burdensome assessments of self-reported health, as well as other sociodemographic factors, did not improve upon the model performance a final model was selected with the easiest to obtain and universally reproducible predictors.

This work has several limitations. This study only accounted for a limited set of 8 of the Charlson Comorbidity Index conditions, and thus there may be several conditions such as end stage renal disease, liver failure, and peptic ulcer disease, among others

which contribute to mortality risk but could not be accounted for in the SEER-MHOS data. This may limit the model's ability to discriminate between individuals likely to survive vs. die, to the extent the missing conditions provide information not already incorporated in the five model factors (such as general health). Overall, the model's performance achieved modest clinical utility for discrimination with c-index values  $>0.70$ .<sup>72</sup> While discrimination improved over prior models, the gains were also relatively modest. However, it should be noted that a third to a half of patients with PCa die of events which may be relatively unpredictable over 10 years (e.g., subsequent development of other non-PCa cancers, acute cardiac events and stroke) with a single set of baseline data.<sup>2,33</sup> Thus there may be inherent limits to the extent to which prognostic models such as the one developed in this study can accurately predict 10-year mortality risk and discriminate between all individuals who will die and survive. This model was also estimated in patients  $<80$ , as clinical decisions regarding treatment are most relevant in that population, which may limit the generalizability of risk estimates to older samples. However sensitivity analysis in older patients suggested the model generalizes well when including older individuals.

## CONCLUSIONS

This study provides a prognostic model which utilizes a simple set of five pretreatment self-reported characteristics that may better identify patients at higher risk of non-PCa mortality than age and comorbidity based assessments alone.

Table 4.1: Patient characteristics

|  | Total       | Prostate-Specific Death | Other Cause Mortality | Surviving   | p-value |
|--|-------------|-------------------------|-----------------------|-------------|---------|
| <b>No. of patients (%)</b>                               | 2425        | 76 (3)                  | 465 (19)              | 1884 (78)   | -       |
| <b>Mean age at diagnosis</b>                             | 72.9        | 74.5                    | 73.8                  | 72.6        | <0.001  |
| <b>Race/ethnicity (%)</b>                                |             |                         |                       |             |         |
| White  | 1879 (77)   | 57 (75)                 | 371 (80)              | 1451 (77)   | 0.282   |
| Black  | 290 (12)    | ~                       | 55 (12)               | 223 (12)    |         |
| Hispanic/Asian/Pacific Islander or other                 | 256 (11)    | ~                       | 39 (8)                | 210 (11)    |         |
| <b>Charlson Comorbidity Index Score (%)</b>              |             |                         |                       |             | <0.001  |
| 0  | 1326 (54)   | 31 (40)                 | 177 (38)              | 1118 (59)   |         |
| 1  | 586 (24)    | 18 (24)                 | 130 (28)              | 438 (23)    |         |
| ≥2   | 513 (21)    | 27 (35)                 | 158 (34)              | 328 (17)    |         |
| <b>Marital Status</b>                                    |             |                         |                       |             |         |
| Married vs. all other (%)                                | 1695 (70)   | 48 (63)                 | 292 (63)              | 1355 (72)   | <0.001  |
| <b>Smoker at diagnosis (%)</b>                           | 301 (12)    | 18 (24)                 | 86 (18)               | 197 (10)    | <0.001  |
| <b>Patient Reported Functioning and Wellbeing</b>        |             |                         |                       |             |         |
| PCS (mean, SD)   | 43.5 (10.9) | 41.2 (11.6)             | 40.1 (11.1)           | 44.4 (10.4) | <0.001  |
| MCS (mean, SD)   | 53.3 (9.4)  | 49.3 (10.7)             | 51.5 (10.4)           | 53.9 (8.9)  | <0.001  |
| Physical Functioning - ADL Index (mean, SD) <sup>‡</sup> | 87.8 (15.5) | 83.1 (17.6)             | 83.4 (16.9)           | 89.2 (14.8) | <0.001  |
| General Health (Fair or Poor) (n, %)                     | 521 (22)    | 23 (30)                 | 169 (37)              | 329 (18)    | <0.001  |
| <b>Tumor Grade (%)</b>                                   |             |                         |                       |             | <0.001  |
| Well to Moderately Differentiated                        | 1630 (67)   | 30 (39)                 | 338 (73)              | 1262 (67)   |         |
| Poorly Differentiated or Unavailable*                    | 795 (33)    | 46 (61)                 | 127 (27)              | 622 (33)    |         |
| <b>Tumor Clinical T-Stage (%)</b>                        |             |                         |                       |             | <0.001  |
| cT1  | 1,193 (49)  | 20 (26)                 | 227 (49)              | 939 (50)    |         |
| cT2  | 819 (34)    | 34 (45)                 | 136 (29)              | 649 (34)    |         |
| cT1/T2 or T3a or Unavailable**                           | 413 (17)    | 22 (29)                 | 102 (22)              | 296 (16)    |         |
| <b>Primary Prostate Cancer Management (%)</b>            |             |                         |                       |             | <0.001  |
| Conservative   | 794 (33)    | 46 (60)                 | 197 (42)              | 551 (29)    |         |
| Radical Prostatectomy                                    | 323 (13)    | ~                       | 28 (6)                | 294 (16)    |         |
| Radiation Therapy  | 1308 (54)   | 29 (38)                 | 240 (52)              | 1039 (55)   |         |

~ cell size <11 individuals for some sub-categories, exact n=, % not reportable per SEER-MHOS data use agreements; the race variable was utilized as five levels in all analyses, including white, black, Hispanic, Asian-Pacific Islander, or other.

\*The small percentage of ungraded tumors were not reported individually in this table due to cell size reporting limitations and represented <3% of the total sample.

\*\*cT3a tumors contributed less than 2% to all categories; exact numbers were not reportable per SEER-MHOS data use agreements. Those without detailed cT-stage available (<3% of the sample) did not have regionalized/metastasized tumors, as confirmed by other SEER staging variables.

<sup>‡</sup>PF-ADL is scored on a 0-100 point scale with 0 being worse and 100 being best and is not normalized to a mean of 50 points

**Table 4.2: Final adjusted Fine and Gray proportional hazards model for 10-year other cause mortality**

| Predictor   | $\hat{\beta}$ | Sub Hazard Ratio | 95% Confidence Interval | Z-Score | p-value for SHR |
|---|---------------|------------------|-------------------------|---------|-----------------|
| <b>Age at diagnosis</b> (1 year increments)   | 0.078         | <b>1.08</b>      | 1.06-1.11               | 6.44    | <0.001          |
| <b>Charlson Comorbidity Index Score</b>   | 0.197         | <b>1.21</b>      | 1.14-1.30               | 6.04    | <0.001          |
| <b>Self-rated general health</b>  |               |                  |                         |         |                 |
| Poor vs. (excellent/very good/good)   | 1.010         | <b>2.75</b>      | 1.83-4.13               | 5.47    | <0.001          |
| Fair vs. (excellent/very good/good)   | 0.623         | <b>1.86</b>      | 1.49-2.33               | 4.84    | <0.001          |
| <b>Smoker at diagnosis</b>  | 0.530         | <b>1.70</b>      | 1.32-2.18               | 4.15    | <0.001          |
| <b>Marital status (all other vs. married)</b>   | 0.307         | <b>1.36</b>      | 1.12-1.66               | 3.04    | 0.002           |
| <i>Baseline Survival: 0.99948996</i>  |               |                  |                         |         |                 |
| <i>10-Year Overall Cumulative Incidence of Non-Prostate Mortality: 24.307%</i>                |               |                  |                         |         |                 |
| <i>Model Harrell's c-index: 0.701</i>   |               |                  |                         |         |                 |
| <i>Over the observation period, the total number of OCM deaths =465. Total PCSM deaths=76</i> |               |                  |                         |         |                 |



**Table 4.3: Range of 10-year other cause mortality risk predictions from competing risks model and recalibration to higher risk patient data**

| Risk Group  | Mean Predicted % 10-Year Non-Prostate Mortality Risk |  |
|-------------|--|--|
|             | SEER-MHOS Data                                       | Social Security Life Table Re-calibrated |
| Lowest 10%  | 12   | 20                                       |
| Lowest 25%  | 15   | 25                                       |
| Median Risk | 20   | 33                                       |
| Highest 75% | 29   | 44                                       |
| Highest 90% | 42   | 61                                       |

Risk scores were calculated as  $1 - (\text{base survival})^{\exp(\sum \hat{\beta}x)}$

Base survival was 0.99948996 for the SEER-MHOS data calculations and 0.999115237 for the Social Security life table re-calibrated estimates.  $\sum \hat{\beta}x$  can be calculated as the sum of the ( $\hat{\beta}$  presented in table 4.2 times the value for the covariate).

**Table 4.4: Sample clinical scenarios with increasing 10-year other cause mortality risk**

|               |  |                  | 10-Year Other Cause Mortality Risk (%) |                           |
|---------------|--|------------------|--|---------------------------|
| Case Risk     | Case Description   | Age at Diagnosis | Low Range Risk Estimate*               | High Range Risk Estimate* |
| Lowest        | A non-smoker who is married, rates health as "good" with CCI score of 0  | 65               | 8                                      | 13                        |
|               |  | 70               | 12                                     | 19                        |
|               |  | 75               | 17                                     | 27                        |
|               |  | 80               | 24                                     | 37                        |
| Lower         | A non-smoker who is married, rates health as "good", with CCI score of 1 | 65               | 10                                     | 16                        |
|               |  | 70               | 14                                     | 23                        |
|               |  | 75               | 20                                     | 32                        |
|               |  | 80               | 28                                     | 43                        |
| Moderate      | Smoker who is married, rates health as "fair", with CCI score of 1       | 65               | 25                                     | 43                        |
|               |  | 70               | 38                                     | 56                        |
|               |  | 75               | 50                                     | 70                        |
|               |  | 80               | 65                                     | 84                        |
| Moderate High | Smoker who is married, rates health as "poor", with CCI score of 2       | 65               | 44                                     | 63                        |
|               |  | 70               | 57                                     | 77                        |
|               |  | 75               | 72                                     | 89                        |
|               |  | 80               | 85                                     | 96                        |
| High          | Smoker who is unmarried, rates health as "poor", with a CCI score of 3   | 65               | 61                                     | 81                        |
|               |  | 70               | 76                                     | 91                        |
|               |  | 75               | 88                                     | 97                        |
|               |  | 80               | 95                                     | 99                        |

\*Low range risk estimates are derived from SEER-MHOS model, high range estimates are derived from the Social Security life table re-calibrated model.

Risk scores were calculated as  $1 - (\text{base survival})^{\exp(\sum \hat{\beta}x)}$

Base survival was 0.99948996 for the SEER-MHOS data calculations and 0.999115237 for the Social Security life table re-calibrated estimates.  $\sum \hat{\beta}x$  can be calculated as the sum of the ( $\hat{\beta}$  presented in Table 4.2 times the value for the covariate).

CCI= Charlson Comorbidity Index

**Supplementary Appendix 4.A: Refitting of prediction model in patients age 66 and older**

Secondary analyses included refitting of the final regression model in patients age 66 and older at prostate cancer diagnosis in order to assess the performance of risk estimates in a population that included older patients. Patient characteristics are detailed in Table 4.A.2. The final model identified in the primary sample was refitted in this older sample to evaluate whether variables performed differently when patients over 80 were included in the sample and to assess to what extent model discrimination changed by including individuals with a high probability of death. The performance of the benchmark models was also re-assessed in this population. Results of these analyses are reported in Table 4.A.2.

Supplemental Table 4.A.1: Patient characteristics: sensitivity analysis (age 66+ group)

|  | Total       | Prostate-Specific Death | Other Cause Mortality | Surviving   | p-value |
|--|-------------|-------------------------|-----------------------|-------------|---------|
| <b>No. of patients (%)</b>                               | 2854        | 116 (4)                 | 648 (23)              | 2090 (73)   | -       |
| <b>Mean age at diagnosis</b>                             | 75.1        | 78.8                    | 77.3                  | 74.3        | <0.001  |
| <b>No. race/ethnicity (%)</b>                            |             |                         |                       |             |         |
| White  | 2221 (78)   | 90 (78)                 | 524 (81)              | 1607 (77)   | 0.09    |
| Black  | 311 (11)    | 13 (11)                 | 66 (10)               | 232 (11)    |         |
| Hispanic/Asian/Pacific Islander or other                 | 322 (11)    | 13 (11)                 | 58 (9)                | 251 (12)    |         |
| <b>Charlson Comorbidity Index Score (%)</b>              |             |                         |                       |             | <0.001  |
| 0  | 1582 (55)   | 50 (43)                 | 259 (40)              | 1273 (61)   |         |
| 1  | 674 (24)    | 27 (23)                 | 172 (27)              | 475 (23)    |         |
| ≥2   | 598 (21)    | 39 (34)                 | 217 (33)              | 342 (16)    |         |
| <b>Marital Status</b>                                    |             |                         |                       |             |         |
| Married vs. all other (%)                                | 1948 (68)   | 69 (59)                 | 390 (60)              | 1489 (71)   | <0.001  |
| <b>Smoker at diagnosis (%)</b>                           | 301 (12)    | 18 (24)                 | 86 (18)               | 197 (10)    | <0.001  |
| <b>Patient Reported Functioning and Wellbeing</b>        |             |                         |                       |             |         |
| PCS (mean, SD)   | 43.5 (10.9) | 41.2 (11.6)             | 40.1 (11.1)           | 44.4 (10.4) | <0.001  |
| MCS (mean, SD)   | 53.3 (9.4)  | 49.3 (10.7)             | 51.5 (10.4)           | 53.9 (8.9)  | <0.001  |
| Physical Functioning - ADL Index (mean, SD) <sup>‡</sup> | 87.8 (15.5) | 83.1 (17.6)             | 83.4 (16.9)           | 89.2 (14.8) | <0.001  |
| General Health (Fair or Poor) (n, %)                     | 521 (22)    | 23 (30)                 | 169 (37)              | 329 (18)    | <0.001  |
| <b>Tumor Grade</b>                                       |             |                         |                       |             | <0.001  |
| Well to Moderately Differentiated                        | 1833 (64)   | 30 (39)                 | 338 (73)              | 1351 (65)   |         |
| Poorly Differentiated or Unavailable*                    | 1021 (36)   | 46 (61)                 | 127 (27)              | 739 (35)    |         |
| <b>Tumor Clinical T-Stage</b>                            |             |                         |                       |             | <0.001  |
| cT1  | 1,372 (48)  | 37 (32)                 | 302 (47)              | 1033 (49)   |         |
| cT2  | 981 (34)    | 46 (39)                 | 191 (29)              | 744 (36)    |         |
| cT1/T2 or T3a or Unavailable**                           | 501 (18)    | 33 (28)                 | 155 (24)              | 313 (15)    |         |
| <b>Prostate Cancer Management</b>                        |             |                         |                       |             |         |
| Conservative   | 1148 (40)   | 83 (71)                 | 356 (54)              | 709 (34)    | <0.001  |
| Radical Prostatectomy                                    | 300 (11)    | ~                       | 26 (4)                | 273 (13)    |         |
| Radiation Therapy  | 1406 (49)   | ~                       | 266 (41)              | 1108 (53)   |         |

~ cell size <11 individuals for some sub-categories, exact n=, % not reportable per SEER-MHOS data use agreements; the race variable was utilized as five levels in all analyses, including white, black, Hispanic, Asian-Pacific Islander, or other.

Mean follow-up time for this cohort was 7.2 years

\*The small % of ungraded tumors were not reported individually in this table due to reporting limitations and represented <3% of the total sample.

\*\*cT3a tumors contributed less than 2% to all categories; exact numbers were not reportable per SEER-MHOS data use agreements. Those without detailed cT-stage available (<3% of the sample) did not have regionalized/metastasized tumors, as confirmed by other SEER staging variables.

<sup>‡</sup>PF-ADL is scored on a 0-100 point scale with 0 being worse and 100 being best and is not normalized to a mean of 50 points

**Supplemental Table 4.A.2: Final adjusted Fine and Gray proportional hazards model for 10-year other cause mortality in men >66 years of age**

| Predictor  | $\hat{\beta}$ | Adjusted Sub Hazard Ratio | 95% Confidence Interval | Z-Score | p-value for Adjusted SHR |
|--|---------------|---------------------------|-------------------------|---------|--------------------------|
| <b>Age at diagnosis</b> (1 year increments)                                    | 0.079         | <b>1.08</b>               | 1.07-1.10               | 10.93   | <0.001                   |
| <b>Charlson Comorbidity Index Score</b>  | 0.199         | <b>1.22</b>               | 1.15-1.29               | 6.81    | <0.001                   |
| <b>Self-rated general health</b>   |               |                           |                         |         |                          |
| Poor vs. (excellent/very good/good)  | 0.709         | <b>2.03</b>               | 1.37-3.00               | 3.55    | <0.001                   |
| Fair vs. (excellent/very good/good)  | 0.465         | <b>1.59</b>               | 1.32-1.92               | 4.81    | <0.001                   |
| <b>Smoker at diagnosis</b>   | 0.536         | <b>1.71</b>               | 1.37-2.13               | 4.78    | <0.001                   |
| <b>Marital status (all other vs. married)</b>                                  | 0.275         | <b>1.32</b>               | 1.11-1.56               | 3.20    | 0.001                    |
| <i>Baseline Survival: 0.999486195</i>  |               |                           |                         |         |                          |
| <i>10-Year Overall Cumulative Incidence of Non-Prostate Mortality: 28.367%</i> |               |                           |                         |         |                          |
| <i>Model Harrell's c-index: 0.724</i>  |               |                           |                         |         |                          |

## CHAPTER V: DISCUSSION AND CONCLUSIONS

This dissertation characterizes the need for OCM risk estimation in older men newly diagnosed with localized PCa and informs efforts to utilize risk estimation tools to better identify patients most likely to benefit from aggressive treatment vs. those who may not. Nearly a quarter of older men who were primarily treated with radiotherapy were overtreated for their PCa. Health factors indicative of a shorter life expectancy had little to no association with radiotherapy assignment, suggesting a need to more carefully assess these factors prior to treatment. However, existing tools for estimating patients' mortality risk require improvement before clinicians can rely on their estimates to make better individualized treatment decisions. A new risk model developed here, with age, comorbidity, self-rated health, smoking, and marital status predictors improved upon prior models' performance for individualized OCM risk estimation, more accurately discriminating between individuals who die and those who do not. While this new model may aid clinicians in better assessing patients' OCM risk, a large percent of OCM deaths remain difficult to predict and future gains in model performance are only likely if improved predictors for these events become available.

### **Overtreatment and improving patient selection for radiotherapy**

Evidence from this dissertation and multiple recent studies now demonstrate that PCa overtreatment among older men is mostly attributable to overtreatment of lower-risk tumors with radiotherapy.<sup>12,14,24</sup> This is primarily due to radiotherapy being far more common among older men than radical prostatectomy (54% vs. 13%, respectively) and because men undergoing radiotherapy are far more likely to die of

OCM in the 10 years following diagnosis than men treated with prostatectomy. It also is clear that health factors play a very different role in the selection of patients for radical prostatectomy vs. radiotherapies.<sup>24</sup> The lack of association between health factors and radiotherapy assignment indicates that there is a clear need for systematic consideration of these factors prior to treatment. Anecdotal evidence from clinicians suggests that older patients are often considered for radiotherapy as they are deemed less optimal surgical candidates.<sup>12</sup> Among these patients, the use of prediction tools will be especially important for separating those likely to die of OCM within 10 years from those who will not.

This dissertation also revealed that overtreatment rates among older men were much lower than previously suggested, although they remain substantial.<sup>15</sup> Previous studies have reported that up to 54-67% of older men with comorbidities may be overtreated,<sup>12,22</sup> however population-based assessments of the overall rates of overtreatment among radiotherapy and prostatectomy treated patients have not yet been reported.<sup>12,14,15,22</sup> In the present study, 23% of men died of OCM over the 10 years following radiotherapy treatment, while only 12% of radical prostatectomy treated men experienced OCM over the same period. This is the first study to report observed average 10-year OCM rates by treatment type among older men in the U.S. At the aggregate level, it appears that overtreatment rates are substantially lower than previously suggested. Differences may in part be due to the fact that some prior studies predicted 10-year OCM risk as opposed to reporting observed cumulative incidences, potentially overestimating mortality risk and thus overtreatment.<sup>22</sup> However, it also remains possible that the overtreatment rates reported here are somewhat biased downward due to the population of men studied.

Medicare managed care plan participants are of better health than other men of similar age, and thus less likely to experience OCM.<sup>66</sup> Nonetheless, the substantial rate of overtreatment among radiotherapy treated patients reported here highlights the need for systematic evaluation of health prior to treatment.

### **Limitations of current mortality risk estimation tools**

While there is a need for accurate assessment of OCM in a pre-treatment clinical setting, available tools have limited clinical utility. This dissertation's evaluation of existing mortality prediction tools for men with PCa revealed that current risk estimation tools have two primary flaws that limit their applicability in a clinical setting; the risk estimates provided by the model vary when applied in different populations, often providing overestimates of true OCM risk, and existing models are limited in their ability to distinguish between patients who will die and those who will not. Current clinical care guidelines recommend that clinicians utilize Social Security life table derived estimates of 10-year mortality risk for estimating life expectancy.<sup>9</sup> However these estimates significantly over-predicted mortality risk in this cohort of men with PCa and had almost no utility at the individual patient level in discriminating between individuals who died and those who did not. Thus, the findings in this study should caution clinicians against using Social Security-based mortality estimates for estimating life expectancy for their patients with PCa. The OCM risk estimation tools, which incorporated comorbidity as a predictor, performed better by both measures but still below thresholds for making clinically reliable distinctions between individual patients' risk. Thus, additional predictors, beyond age and comorbidity alone, are needed for improving risk predictions.

**Self-rated health and sociodemographic factors improve predictions**

The addition of self-rated health, smoking status and marital status to age and comorbidity predictors improved risk estimates. These factors capture additional information that is distinct from either age or comorbidity and improve the ability to discriminate between individual patients who will die versus those who will not. Each of these factors are well established predictors of mortality risk.<sup>27,33,37,41,77,79</sup> While these may appear to be a limited set of predictors, the final risk estimation model presented in Chapter IV performed as well as models which included more burdensome evaluations of health such as multiple activities of daily living and more comprehensive assessments of patient-reported health from the SF-36 and VR-12 health surveys.

The prediction model developed in this dissertation has the advantage of relying exclusively on self-reported data for OCM risk estimation. These variables are easy to obtain in any clinical setting. For example, the self-rated health variable is a simple five level rating of overall general health from excellent to poor; questions about current smoking status at diagnosis and whether the individual is married or not are equally low-burden to obtain. Comorbid conditions are limited to a finite number of conditions that can also be rapidly obtained.

This information can easily be integrated to generate OCM risk estimates with the risk estimation tool developed in this dissertation. The tool provides a range of risk estimates to illustrate the potential variability in estimated risk between different populations of patients, intended to improve the generalizability of the risk estimates. Clinicians can see that a 70 year old married, non-smoking man, who has a CCI score of 1 and rates his health as fair may have a 48-67% risk of OCM, for example.



This addresses one of the main limitations of prior models, which provide single point estimates of risk that can often over-or under-predict OCM risk. This dissertation provides a low-range estimate using the SEER-MHOS data and re-calibrated estimates to match death rates expected for age-matched males in the U.S. general population as a higher-range OCM risk estimate. Risk estimates can be interpreted in relation to the distribution of risk in the population, placing the example patient above into the highest 90% of OCM risk and suggesting that this patient would not benefit from definitive PCa treatment.

**Limitations to prediction: the predictable vs. unpredictable**

Many men with PCa go on to die of medical conditions that were not identified at the time of PCa diagnosis. Up to a quarter of men with PCa die of other cancers, most of which are diagnosed after their PCa.<sup>2,33</sup> Another quarter of deaths in men with PCa are attributable to cardiac causes, many of which may acutely lead to death such as myocardial infarction, endocarditis, or are conditions which often lead to a demise in <10 years (such as heart failure).<sup>2,33</sup> The lack of good predictors for many causes of death, as well as the subsequent development of diseases not present at baseline, limits the extent to which perfect discrimination between patients who will die from those who survive 10 years can be achieved. It is difficult to predict deaths from these causes in the absence of information about these conditions. Perhaps more complex models that predict the likelihood of developing these diseases and incorporates that risk in OCM risk estimation would be of benefit. However, there are inherent limitations to predicting the occurrence of other cancers as most are due to unexplained random variation, and our ability to predict the acute cardiac events that lead to death is also relatively limited.<sup>80</sup> Ultimately, predicting an

outcome such as OCM, which is influenced by many factors, at such a distant end point (10 years), during decades of life where health can change rapidly, may have inherent limitations.

Yet despite these limitations, this dissertation demonstrated that clinicians are in fact relatively capable of selecting healthy patients with over 10-year life expectancy for treatment. This was clearly true for patients treated with radical prostatectomy, who died of OCM at a relatively low rate. This is likely largely driven by the fact that younger men are selected for radical prostatectomy; very few men over the age of 75 undergo this surgery.<sup>12</sup> Furthermore, all of the measured health factors also appear to influence assignment to radical prostatectomy including comorbidity burden, physical health, and smoking. Thus, consideration of these factors in addition to age likely does achieve the goal of reducing overtreatment by selecting patients most likely to have over a 10-year life expectancy. Despite the flaws that some current tools may have in providing optimally precise risk estimates, they may promote discussions surrounding patients' age and health and treatment risks and benefits and thereby help reduce the reflex to treat "cancer," despite its indolent nature.<sup>11,81</sup>

### **The future of OCM risk estimation**

As the collection of patient-reported health data becomes more prevalent and is better integrated into the clinical electronic medical record, future OCM prediction models may benefit from the integration of these types of data. Were a comprehensive electronic medical record available, with automatically generated comorbidity scoring information, and automated algorithms for predicting the risk of developing conditions associated with mortality (e.g. acute myocardial infarction),

future OCM risk prediction tools could harness these inputs. This may provide richer baseline health information than is currently available by just utilizing the presence or absence of particular medical conditions at baseline. There also is a wealth of additional patient-reported health information that can help us to better understand comorbidity. Patient report of disease impact and severity may provide a mechanism for distinguishing patients at higher risk of death from particular conditions.<sup>82</sup> Future tools may be able to move beyond static assessments of the presence or absence of a condition and current ratings of health, and may be able to predict the development of comorbidities, which are difficult to comprehensively assess with the current types of databases available for generating prediction models.

## **CONCLUSIONS**

Overtreatment of older men with PCa is primarily due to definitive treatment with radiotherapy and may be reduced by reserving treatment for patients with lower comorbidity burden, better physical health and non-smokers. Implementation of 10-year OCM risk estimation tools in pre-treatment decision-making may aid in reducing overtreatment by promoting consideration of these health factors. Existing age and comorbidity-based tools for 10-year OCM risk estimation are improved upon by the addition of self-reported health, marital and smoking status at diagnosis. This set of five pretreatment self-reported characteristics may better identify patients who will die of OCM and those who will not.

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