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14. ABSTRACT

Men with biochemical recurrence after definitive therapy for prostate cancer are often treated with early androgen deprivation therapy (ADT) despite a lack of clear evidence of survival benefit. Early ADT is especially risky for older men or those with multiple comorbidities, since it significantly increases risk of cardiovascular mortality in these men. Moreover, as the putative survival advantage associated with early ADT is not realized for many years, for older and sicker men, it is likely that any survival benefit of early ADT is markedly attenuated due to limited longevity. Though an argument could be made for delaying hormonal therapy in these men (especially those with favorable tumor risk characteristics), such a paradigm has yet to be realized due to lack of compelling data.
Hypothesis/Objective: We will use the Shared Equal Access Regional Cancer Hospital (SEARCH) database, a nationally representative database of men with prostate cancer treated with radical prostatectomy across 6 VA medical centers, to characterize the impact of age, comorbidity, and tumor risk on competing risks for mortality, treatment variation, and treatment effectiveness in men with biochemical recurrence after radical prostatectomy. This database was developed by and run for the past 16 years by my collaborator, Dr. Stephen Freedland. We hypothesize that: (1) the competing risk of non-cancer mortality will greatly outweigh the risk of cancer mortality in older and/or sicker men with favorable tumor risk; (2) age and comorbidity will have little impact on use of early ADT in men with biochemical recurrence regardless of tumor risk; and (3) the survival benefit from early ADT will be diminished in older and sicker men compared with those who are younger and healthier.

15. SUBJECT TERMS
Prostate cancer, Androgen deprivation therapy (ADT)

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1. **INTRODUCTION:**

Timing of androgen deprivation therapy (ADT) for biochemical recurrence (BCR) after definitive treatment of prostate cancer is controversial, given its morbidity and the dubious survival benefit of early ADT. Older and sicker men have higher risks of morbidity and mortality with ADT. Moreover, as the putative survival advantage associated with early ADT is not realized for many years, for older and sicker men, it is likely that any survival benefit of early ADT is markedly attenuated due to limited longevity. The overall purpose of this study is to use a nationally representative dataset of men with recurrent prostate cancer across 8 VA medical centers to characterize the impact of age, comorbidities, and tumor-related variables on: (1) the timing of ADT; (2) long-term risks of dying of prostate cancer vs. other causes in men with BCR; and (3) the benefits of early ADT vs. delayed/no ADT to improve survival. The reporting period for this study covers progress made toward **Aims 1 and 2.**

2. **KEYWORDS:**

Androgen Deprivation Therapy; Health Services Research; Comorbidity; Age; Prostate Cancer

3. **ACCOMPLISHMENTS:**

- **What were the major goals of the project?**

The specific aims of the projects are:

Aim 1: To characterize variation in treatment regarding use of early vs. delayed hormonal therapy in men with recurrent disease across age, comorbidity, and tumor risk subgroups.

Aim 2: To determine the competing risks of long-term cancer-specific and other-cause mortality in men with recurrent disease across age, comorbidity, and tumor risk subgroups.

Aim 3: To compare cancer-specific and overall mortality among men treated with early vs. delayed hormonal therapy across age, comorbidity, and tumor risk subgroups.

This reporting period covers planned work in the SOW for months 24-36 of the award period: manuscript submission and data dissemination for **Aim 2** and statistical analysis, data interpretation, manuscript preparation for **Aim 3**.

- **What was accomplished under these goals?**

(1) Objectives: Over this reporting period on the SOW, for **Aim 1** we had planned to re-submit the manuscript for publication. For **Aim 2** we had planned to finalize our manuscript (months 24-27), submit for peer-reviewed publication (month 27), and present findings. For **Aim 3**, we had planned to conduct statistical analysis (months 27-30), interpret results (months 30-33), prepare a manuscript (months 33-36), and submit the manuscript (month 36).

(2) Major activities: Regarding **Aim 1,** in the last annual report, we had reported that we had submitted a manuscript describing variation in use of ADT by age and comorbidity to a peer-reviewed journal. Since that time, the manuscript has been accepted and published at *Urology* Practice, one of the official peer-reviewed journals of the AUA (article included as an attachment). Regarding **Aim 2,** we finalized the manuscript, submitted it to a peer-reviewed journal, published the results in *Journal of Urology*, the main peer-reviewed journal of the AUA, and presented the results virtually at a podium session of the 2020 AUA Annual Meeting. Regarding **Aim 3**, we conducted the statistical analysis and interpreted results. Unfortunately, we did not find our expected results due to what we think is due to limitations related to our approach, so we applied for an NCE for 1 year to allow us further time to conduct additional analyses to achieve our goals.

(3) Significant results:

- For **Aim** 1, our results are described in full in the attached published article in **Appendix 1**. Key findings from this analysis were:

- Across 2,097 men with biochemical recurrence after radical prostatectomy, median PSA at ADT initiation was 6.2ng/ml (95%CI 5.1–7.1) across all patients, but differed among those who received adjuvant/salvage radiation (3.6ng/ml, 2.8–4.3) and those who did not (12.1ng/ml, 9.6–15.2) (p<0.001) **(Appendix 1, Figure 1)**.
- In multivariable Cox regression, advanced age (p=0.03) but not worse comorbidity (p=0.25) was associated higher PSA at initiation of ADT (**Appendix 1, Table 2**). For example, PSA at ADT was lower among those <60 years (3.7ng/ml, 2.6–5.8) compared with those 60–64 (5.0ng/ml, 3.9–6.6), 65–69 (6.6ng/ml, 4.9–8.8), 70–74 (8.8ng/ml, 6.1–12.3), and ≥75 (14.1ng/ml, 5.5–37.8) (**Appendix 1, Figure 2a**). In contrast, PSA at ADT was similar among comorbidity subgroups (e.g. CCI0 (6.3ng/ml, 5.0–7.9) vs. CCI3+(5.6ng/ml, 4.1–7.4)) (**Appendix 1, Figure 3a**). These results were consistent across men who received salvage XRT and those who did not (**Appendix 1, Figure 2bc, Figure 3bc**).

- For **Aim 2**, our results are described in full in the attached published article in **Appendix 2**. Key findings from this analysis were:
  - Of the 1,225 men in our sample, 243 (20%) died of other causes, 68 (6%) died of prostate cancer over median follow up of 5.6 years (IQR 2.7, 9.1).
  - Multivariable competing risks regression showed that higher preoperative D'Amico tumor risk and PSA-DT at BCR <9 months were associated with both PC metastasis and mortality (all p≤0.001). Advanced age and worse comorbidity burden were associated with other-cause mortality (both p≤0.001) (**Appendix 2, Table 1**).
  - Competing risks regression plots showed cumulative incidence of prostate cancer metastasis and mortality over time by key clinical predictors. For example, men with PSA-DT at BCR < 9 months had 16% and 9% cumulative incidence of metastasis and PC mortality at 10 years (**Appendix 2, Figure 1**).
  - Competing risks regression plots showed cumulative incidence of other-cause mortality over time by key clinical predictors. For example, cumulative incidence of 10-year other-cause mortality was substantially higher among men 70 years or older with CCI 1 (45%), 2 (40%), or 3+ (49%) compared with those with CCI 0 (20%) (**Appendix 2, Figure 2**).
  - Recursive partitioning analysis (RPA) identified optimal variable cutpoints for prediction of prostate cancer mortality (**Appendix 2, Figure 3**)—PSA at recurrence (<10 vs. ≥10 ng/ml), D'Amico tumor risk (low/intermediate vs. high), and PSA doubling time (<9 vs. ≥9 months)—with the highest risk subgroup having 10-year PCSM of 22%. RPA identified optimal variable cutpoints for prediction of other-cause mortality (**Appendix 2, Figure 3**)— age at BCR (<70 vs. ≥70 years), and CCI at BCR (for those <70, CCI<2 vs. ≥2; for those ≥70, CCI0 vs. ≥1)—with the highest risk subgroup having 10-year OCM of 51% (**Appendix 2, Figure 3**).
  - We concluded that these competing risks estimates for prostate cancer metastasis and mortality as well as other-cause mortality could allow for more individualized prognosis assessment for patients with biochemical recurrence after radical prostatectomy.

- For **Aim 3**, we investigated comparative effectiveness of early vs delayed ADT among age, comorbidity, and tumor risk subgroups, with the hypothesis that early ADT would be less effective in patients who were highly likely to die of other causes within 10 years and had low-risk tumors. We conducted Cox regression analysis with sequential stratification (method used to account for selection bias) to compare survival outcomes in subgroups of age, comorbidity, and tumor risk. Key findings from this analysis were:
  - Of 1,385 men in our sample, 336 (24%) received early ADT. Overall, early ADT patients were younger (63 years vs. 65 years), more often had a lower PCCI score (PCCI ≤4 61% vs. 55%), more often had a high D'Amico risk (49% vs. 35%), more often received radiation (73% vs. 48%), and had longer follow-up time after recurrence (72.9 months vs. 64.2 months). (**Appendix 3, Table 1, Figure 1**)
  - We conducted sequential stratification to match each patient who received early ADT with 5 patients who received delayed ADT at the same PSA level (<= 2.5 +/- 0.5 ng/ml), date of BCR (+/- 2 years), PCCI category (0-4, 5+), and D'Amico risk category (high, intermediate, and low risk). After sequential stratification, the matched controls had similar distributions of year of

recurrence, PCCI group, D'Amico risk, and PSA at recurrence compared with those receiving early ADT. (**Appendix 3, Table 2**)

- At the end of the follow-up period, there were 74 deaths among the early ADT patients (n=336, median follow up time 58.4 months) and 206 deaths among the delayed ADT matches (n=1,680, median follow-up time 42.1 months).
- We first attempted to compare risks of cancer-specific mortality between early ADT and matched delayed ADT groups, but we were unable to do this due to a limited number of prostate cancer deaths. We therefore decided to analyze overall mortality.
- In the multivariable model looking at all patients, early ADT was associated with an increased risk of death from any cause (HR=1.49, 95% CI 1.07, 2.08, p=0.02). In subgroup analysis, early ADT was associated with a statistically significant increase in risk of death from any cause among patients with PCCI ≤4 (HR=1.72, 95% CI 1.11-2.67, p=0.02) and trend towards an increase in risk of death from any cause in those with low/intermediate D'Amico risks (HR=1.49, 95% CI 0.99-2.26, p=0.06). No statistically significant associations were found within PCCI ≥5 and high D'Amico risk subgroups, but direction and magnitude of effect were similar to those with lower PCCI scores. (**Appendix 3, Table 3**)
- We conducted analysis to confirm that 5 matches for each patient optimized stability of estimates compared with lower or higher number of matches. (**Appendix 3, Figure 2, Supplementary Tables 1a-f**)

- **What opportunities for training and professional development has the project provided?**
  - Mentorship in data analysis and manuscript preparation under Dr. Freedland
  - Development in mentorship skills to trainees in working with resident in Urology Dr. Ariel Moradzadeh (Cedars-Sinai) (**Aim 1**) and Masters in Biostatistics candidate→degree designate Allison Reagan (Duke).
  - Presentation of results at AUA National meetings in 2018 and 2020.
  - Further development of skills in cutting edge techniques such as recursive partitioning analysis

- **How were the results disseminated to communities of interest?**

  Results for **Aim 1** were reported to the urologic community at the 2018 AUA Annual Meeting (Moderated Poster Session, General & Epidemiological Trends & Socioeconomics: Practice Patterns, Quality of Life, and Shared Decision Making Session, San Francisco, CA May 2018) and the 2018 LA Urological Society Annual Resident Research Forum (Los Angeles, CA; June 2018). Results were published in the peer-reviewed journal *Urology Practice*.

  Results for **Aim 2** were reported to the urologic community at the 2020 AUA Annual Meeting (Virtual podium presentation, Prostate Cancer: Epidemiology Session, May 2020). Results were published in the peer-reviewed *Journal of Urology*.

- **What do you plan to do during the next reporting period to accomplish the goals?**

  In the next reporting period as part of our NCE, we plan to continue work on **Aim 3**, which involves testing comparative effectiveness of early vs. delayed ADT in reducing cancer-specific and overall mortality across groups of men most and least likely to benefit from early ADT identified in Aim 2. We plan to further refine our models to better analyze cancer-specific outcomes; for example, we will use recursive partitioning to identify characteristics associated with benefit of early vs delayed ADT.

IMPACT:

- **What was the impact on the development of the principal discipline(s) of the project?**

For **Aim 1**: In our study, we found that men with significant comorbid disease burdens who develop BCR after radical prostatectomy often receive ADT at relatively low PSAs. Though age appears to strongly affect timing of ADT—with older men receiving ADT at slightly higher PSA values than younger men—comorbidity has little effect on timing of ADT, even among men with lower tumor risk. Since men with significant comorbidity are most likely to be harmed by ADT, we hope that these data will help to spur clinicians to delay ADT in these men unless they are at high risk for progression.

For **Aim 2**: In our study, we quantified the long-term competing risks of prostate cancer metastasis/mortality and other-cause mortality in men with BCR after radical prostatectomy across their key clinical predictors. We also empirically identified optimal risk stratification cutpoints for these key variables to define subgroups of men who are most likely to die of other causes and, conversely, prostate cancer. This information will improve precision of prognosis for men with BCR after radical prostatectomy and allow for more individualized prediction of metastasis and mortality across readily available clinical variables. Importantly, it will also inform further study of efficacy of early versus delayed ADT in men who may be more or less likely to benefit from these therapeutic approaches; we believe that older men with comorbidity burden who are currently receiving early ADT may benefit from a delayed approach, given the protracted timecourse of survival benefit of early ADT and its immediate morbidity.

For **Aim 3**, we had hoped to prove that early ADT is less beneficial for patients with higher risk of death from other causes and lower risk of death from prostate cancer. However, limitations in event rate for prostate cancer deaths in subgroups of age, comorbidity, and cancer risk made assessment of cancer-specific outcomes unreliable with our planned methodology. Analysis of overall mortality suggested no differences in overall mortality between those treated with early ADT vs delayed ADT in subgroups of comorbidity and tumor risk. These results are contrary (or at least null) to our hypothesis, and we believe they may be related to our model structure. We plan to refine our approach over the coming year using an alternative method involving recursive partitioning analysis.

- **What was the impact on other disciplines?**

Nothing to report

- **What was the impact on technology transfer?**

Nothing to report

- **What was the impact on society beyond science and technology?**

Nothing to report

- **CHANGES/PROBLEMS:**

- **Changes in approach and reasons for change**

For **Aim** 3, we had hoped to prove that early ADT is less beneficial for patients with higher risk of death from other causes and lower risk of death from prostate cancer. However, limitations in event rate for prostate cancer deaths in subgroups of age, comorbidity, and cancer risk made assessment of cancer-specific outcomes unreliable with our planned methodology. Analysis of overall mortality suggested no differences in overall mortality between those treated with early ADT vs delayed ADT in subgroups of comorbidity and tumor risk. These results are contrary (or at least null) to our hypothesis, and we believe they may be related to our model structure. We plan to refine our approach over the coming year using an alternative method involving recursive partitioning analysis; specifically, we will empirically identify factors associated with improved cancer-specific survival among patients who received early ADT and those who received delayed ADT. We hope to prove that age,

comorbidity, and tumor risk will emerge as predictive factors. We believe that this method will not be as sensitive to the limitations on event rate that our former approach did.

- **Actual or anticipated problems or delays and actions or plans to resolve them**

  Nothing to report

- **Changes that had a significant impact on expenditures**

  Nothing to report

- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

  Nothing to report

- **Significant changes in use or care of human subjects**

  Nothing to report

- **Significant changes in use or care of vertebrate animals.**

  Not applicable.

- **Significant changes in use of biohazards and/or select agents**

  Not applicable.

- **PRODUCTS:**
  - **Publications, conference papers, and presentations**

    - **Conference publications.**

      (1) Moradzadeh A, Howard L, Aronson W, Terris M, Cooperberg M, Amling C, Kane C, Freedland SJ, Daskivich TJ. " The impact of comorbidity and age on timing of androgen deprivation therapy in men with biochemical recurrence after radical prostatectomy." Moderated Poster Presentation, General & Epidemiological Trends & Socioeconomics: Practice Patterns, Quality of Life, and Shared Decision Making Session, American Urological Association 2018 Annual Meeting, San Francisco, CA, May 2018.
      (2) Moradzadeh A, Daskivich TJ. " The impact of comorbidity and age on timing of androgen deprivation therapy in men with biochemical recurrence after radical prostatectomy." Podium Presentation, Los Angeles Urological Society Annual Resident Research Forum, Los Angeles, CA, June 2018.
      (3) Daskivich TJ, Howard LE, Amling C, Aronson W, Cooperberg M, Kane C, Klaasen Z, Terris M, Freedland SJ**.** "Long-Term Competing Risks of Mortality Among Men with Biochemical Recurrence after Radical Prostatectomy." Virtual podium presentation, Prostate Cancer: Epidemiology Session, American Urological Association 2020 Annual Meeting, Virtual Presentation, May 2020.

    - **Journal publications.**

      Moradzadeh A, Howard LE, Freedland SJ, DeHoedt AM, Amling CL, Aronson WJ, Cooperberg M, Kane CJ, Terris MK, **Daskivich TJ**. The Impact of Comorbidity and Age on Timing of Androgen Deprivation Therapy in Men with Biochemical Recurrence after Radical Prostatectomy. In press, *Urology Practice*. Accepted date August 4, 2020. Planned publication date March 2021.

      Daskivich TJ, Howard LE, Amling CL, Aronson WJ, Cooperberg M, Kane CJ, Klaassen Z, Terris MK, Freedland SJ. Competing Risks of Mortality Among Men with Biochemical Recurrence after Radical Prostatectomy. J Urol. 2020 Sep;204(3):511-517. doi: 10.1097/JU.0000000000001036. Epub 2020 Apr 3. PMID: 32243242

    - **Books or other non-periodical, one-time publications.**

      Nothing to report

- **Other publications, conference papers, and presentations.**

  The following publication from our research team used methods similar to those used to accomplish Aim 2:

  Whitney CA, Howard LE, Freedland SJ, DeHoedt AM, Amling CL, Aronson WJ, Cooperberg M, Kane CJ, Terris MK, **Daskivich TJ**. Impact Of Age, Comorbidity, And PSA Doubling Time On Long-Term Competing Risks For Mortality Among Men With Non-Metastatic Castration-Resistant Prostate Cancer. Prostate Cancer and Prostatic Diseases. 2018, Oct. epub before print. doi: 10.1038/s41391-018-0095-0. PMID: 30279582.

  Our research team presented an abstract at the 2018 AUA Annual Meeting noting persistent overtreatment of men with limited life expectancy in the active surveillance era, despite decreased overtreatment of low-risk disease:

  Vaculik K, Luu M, Howard LE, Aronson W, Terris M, Kane C, Amling C, Cooperberg M, Freedland SJ, **Daskivich TJ.** "Time trends in the surgical treatment of Prostate Cancer by Life Expectancy and Tumor Risk in a National VA Cohort." Moderated Poster Presentation, Prostate Cancer: Epidemiology Session, American Urological Association 2019 Annual Meeting, Chicago, IL.

- **Website(s) or other Internet site(s)**

  Nothing to report.

- **Technologies or techniques**

  Nothing to report

- **Inventions, patent applications, and/or licenses**

  Nothing to report

- **Other Products**

  Nothing to report

- **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

- **What individuals have worked on the project?**

Name:	Timothy Daskivich, MD, MS
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	https://orcid.org/0000-0002-7540-3272
Nearest person month worked:	1.2
Contribution to Project:	Dr. Daskivich drafted and submitted the IRB application, ensurede regulatory compliance, directed the research team in collecting key data from the electronic medical record and cleaning the dataset, directed the research team in development of statistical models and interpretation of data, and drafted the manuscript.
Funding Support:	N/A

Name:	Stephen Freedland, MD
Project Role:	Co- Investigator
Researcher Identifier (e.g. ORCID ID):	https://orcid.org/0000-0002-8104-6419
Nearest person month worked:	0.12
Contribution to Project:	Dr. Freedland participated in data analysis, interpretation of results, and manuscript preparation. He also oversaw activities relevant to the study at the Durham VA.
Funding Support:	N/A

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

  No.

- **What other organizations were involved as partners?**

  Durham VA

  - **Organization Name:** Durham VA
  - **Location of Organization:** Durham, NC
  - **Partner's contribution to the projec**t
    - **Collaboration**: Study staff working on project are at the Durham VA, as mentioned in the grant application.

- **SPECIAL REPORTING REQUIREMENTS**

- **COLLABORATIVE AWARDS:**

  Not applicable.

- **QUAD CHARTS:**

  Not applicable.

- **APPENDICES:**

Appendix 1. Published article for Aim 1. "The Impact of Comorbidity and Age on Timing of Androgen Deprivation Therapy in Men with Biochemical Recurrence after Radical Prostatectomy"
Appendix 2. Published article for Aim2. "Competing Risks of Mortality Among Men with Biochemical Recurrence after Radical Prostatectomy"
Appendix 3. Tables and Figures from analyses of Aim 3.

Author's Accepted Manuscript

The Impact of Comorbidity and Age on Timing of Androgen Deprivation Therapy in Men with Biochemical Recurrence after Radical Prostatectomy

Moradzadeh A, Howard LE, Freedland SJ, Amling CL, Aronson WJ, Cooperberg MR, Kane CJ, Klaassen Z, Terris MK, Daskivich TJ

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The Impact of Comorbidity and Age on Timing of Androgen Deprivation Therapy in Men with Biochemical Recurrence after Radical Prostatectomy

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ABSTRACT

Background: Older men with major comorbidities have higher risks of morbidity and mortality from androgen deprivation therapy (ADT), and benefits of immediate ADT after biochemical recurrence (BCR) in these men are unclear. We assessed variation in timing of ADT by age and comorbidity in a cohort of men with BCR after radical prostatectomy (RP).

Methods: We analyzed 2,097 men with BCR after RP from 2000–2017 in the VA Shared Equal Access Regional Cancer Hospital (SEARCH) database. We ascertained age and Deyo-Charlson comorbidity index (CCI) scores at BCR. Kaplan Meier analysis and multivariable logistic regression were used to determine association of age and CCI with PSA at the initiation of ADT.

Results: In Kaplan-Meier analysis with PSA at ADT as the outcome, median PSA at ADT initiation (95% CI) was 6.2ng/ml (5.1-7.1) across all patients, but differed among those who received adjuvant/salvage radiation (3.6ng/ml, 2.8-4.3) and those who did not (12.1ng/ml, 9.6-15.2) ($p<0.001$). In multivariable Cox regression, advanced age ($p=0.03$) but not worse comorbidity ($p=0.25$) was associated higher PSA at initiation of ADT. Across all patients, PSA at ADT was lower among those <60 years (3.7ng/ml, 2.6-5.8) compared with those 60–64 (5.0ng/ml, 3.9-6.6), 65–69 (6.6ng/ml, 4.9-8.8), 70–74 (8.8ng/ml, 6.1-12.3), and ≥75 (14.1ng/ml, 5.5-37.8). In contrast, PSA at ADT was similar among comorbidity subgroups (CCI0(6.3ng/ml, 5.0-7.9) vs. CCI3+(5.6ng/ml, 4.1-7.4)). In general, these relationships were consistent among subgroups receiving adjuvant/salvage radiation.

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Conclusions: Men with comorbid disease at increased risk of morbidity and mortality with ADT often receive ADT at low PSA values.

INTRODUCTION

Androgen deprivation therapy (ADT) is commonly used to treat biochemical recurrence (BCR) after failure of local therapy for prostate cancer, but timing of ADT is controversial due to its uncertain clinical benefit and potential morbidity. Early ADT—initiating ADT at low PSAs, such as <2.5 [1]—has not been consistently shown to improve survival compared with starting at higher PSA values in randomized trials [2, 3], and meta analyses have had conflicting conclusions about the effects of ADT on overall and prostate cancer-specific survival[4, 5], especially among older and sicker men who are at high risk for ADT-related morbidity[6, 7]. ADT also has substantial morbidity: in addition to fatigue, weight gain, hot flashes, decreased libido, and erectile dysfunction[8], ADT increases risk of cardiometabolic diseases (diabetes, coronary heart diseases), cardiac morbidity (e.g. myocardial infarction) [9-11], thromboembolic disease [12], depression[13], and cardiac mortality[5, 14-16]. Despite this, there are no clear guidelines on timing of ADT after BCR, which leaves the physician to balance the benefits and risks of ADT for the individual patient.

Older men with major comorbidities are least likely to benefit and most likely to be harmed by early ADT[7]. Meta-analysis data suggest that the cancer control benefits of ADT may only be realized after many years[4], at which time older and sicker men will

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have already died of causes other than prostate cancer[17, 18]. Observational studies have shown that comorbidity severity worsens in men with pre-existing cardiometabolic conditions such as diabetes [10, 11], and men with cardiovascular comorbidity are at higher risk of mortality even with short courses of adjuvant ADT[16]. For these reasons, experts have urged clinicians to be cautious in using ADT for men with pre-existing comorbidities[19]. However, there is a lack of data on variation in timing of ADT in men with BCR after definitive therapy across groups with varying age and health status to better define current practice patterns.

In this study, we assessed variation in timing of ADT among men with BCR after radical prostatectomy across 6 VA medical centers in the Shared Equal Access Regional Cancer Hospital (SEARCH) database [20]. This cohort is well-suited to answer the question given the higher burden of comorbidities in the VA[21], the availability of longitudinal PSA data, and the minimization of economic influences on service utilization in this non-fee-for-service delivery system[22]. We hypothesized that the timing of ADT would be delayed in older men but not those with worse comorbidity, as has been observed with other health services for prostate cancer.

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MATERIALS AND METHODS

Study population

The SEARCH database includes men with prostate cancer treated with radical prostatectomy from 1988 to 2017 across 8 VA Medical Centers (n=7,811)[23]. We identified men with BCR after RP (defined as: one PSA>0.2 ng/ml; two PSAs of 0.2 ng/ml; or secondary treatment for a rising PSA) who had BCR between 2000–2018 (n=2,475). We excluded men without a known PSA prior to ADT initiation (n=9); those with locally advanced prostate cancer (pT3/4) (n=17); and those with missing clinical stage (n=275), PSA at recurrence (n=10), PSA at diagnosis (n=42), or pathological stage (n=25). Our final study cohort included 2,097 men (Supplemental Figure 1). The study received IRB approval (IRB #00044354).

Variables

Primary predictors

Age at BCR was obtained by review of the electronic medical record and was coded categorically (<60, 60–64, 65–69, 70–74, and ≥75). Deyo-Charlson comorbidity index score (CCI) at BCR (0, 1, 2, 3+) was calculated using inpatient and outpatient claims[24].

Primary outcomes

Categorization of PSA values at ADT in our descriptive characteristics were based on definitions from the literature[1], though PSA at ADT was considered as a continuous

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variable in our main models.

Covariates

D'Amico tumor risk[25], clinical stage, pathologic characteristics (grade, stage, surgical margin, extracapsular extension, seminal vesicle invasion, lymph node involvement), PSA doubling time (PSADT) at BCR[26], and receipt of adjuvant/salvage XRT were ascertained by review of the electronic medical record. Sociodemographic information was also collected, including year of BCR and race/ethnicity.

Statistical analysis

Characteristics of our study population across categorizations of PSA at ADT were compared using Kruskal Wallis and chi-square tests for continuous and categorical variables, respectively.

The association of CCI score and age with PSA at the time of ADT was analyzed using Cox proportional hazards regression. Since we were interesting in the timing of ADT based on PSA value instead of calendar time, we used PSA as the time element in the survival analysis and ADT as the event. Patients who did not receive ADT were censored at their highest PSA value during follow-up. Backwards stepwise selection (removal threshold p=0.10, entry threshold p=0.05) was used to select covariates. Age at ADT and CCI were locked in the model. Candidate covariates are listed in Table 1. The Cox models were repeated in strata of men who did and did not use XRT, who had

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negative lymph nodes, who had PSADT <9 or ≥9, and after including time to BCR as a covariate.

Kaplan-Meier estimates with PSA at ADT as the outcome measure were graphed overall and stratified by XRT use, age, and CCI. Median PSA at ADT initiation was calculated from Kaplan-Meier estimates. Using Kaplan-Meier analysis allows inclusion of all patients regardless of whether or not they received ADT. Subjects were censored at the time of their last PSA measurement.

Statistical analyses were performed using Stata 15.0 (StataCorpLP, College Station, TX) and SAS. A two-sided $p<0.05$ denoted statistical significance.

RESULTS

Sample characteristics by PSA at ADT are noted in Table 1. Forty percent of our sample received ADT (n=837, 40%). In univariable comparisons, ADT tended to be started at lower PSAs among men who were younger and healthier, treated in later years, with positive surgical margins, higher rates of extracapcular extension, seminal vesicle invasion, and lymph node involvement, lower pre-surgical PSA, lower clinical stage, higher pathological grade group, lower PSA at BCR, slower PSADT at BCR, and among those receiving salvage XRT.

In Kaplan-Meier analysis with PSA at ADT initiation as the outcome measure, median PSA at ADT (95% CI) was 6.2ng/ml (5.1-7.1) across all patients (Figure 1a). However,

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PSA at ADT differed among those who received adjuvant/salvage radiation (3.6ng/ml, 2.8-4.3) and those who did not (12.1ng/ml, 9.6-15.2) (p<0.001) (Figure 1b).

Multivariable Cox proportional hazards regression analyzing association of age and comorbidity at BCR with PSA at ADT showed that advanced age (p=0.03) but not worse comorbidity (p=0.25) was associated with higher PSA at initiation of ADT (Table 2). Kaplan-Meier analysis (Figure 2a) showed that across all patients, median (95% CI) PSA at ADT was lower among those <60 years (3.7ng/ml, 2.6-5.8) compared with those 60–64 (5.0ng/ml, 3.9-6.6), 65–69 (6.6ng/ml, 4.9-8.8), 70–74 (8.8ng/ml, 6.1-12.3), and ≥75 (14.1ng/ml, 5.5-37.8). In contrast, PSA at ADT was similar among comorbidity subgroups (e.g. CCI0 (6.3ng/ml, 5.0-7.9) vs. CCI3+(5.6ng/ml, 4.1-7.4) (Figure 3a). These relationships were generally consistent among subgroups receiving adjuvant/salvage radiation (Figures 2b, 3b) and not receiving adjuvant/salvage radiation (Figure 2c, 3c).

Similar associations were seen in subgroups of men who who had negative lymph nodes on surgical pathology, in subgroups of PSADT≥ or <9 months, and after including time to BCR as a covariate (Supplementary Tables 1 and 2).

DISCUSSION

There are currently no guideline recommendations regarding timing of ADT in men with BCR after radical prostatectomy, reflecting the difficulty balancing of known risks with uncertain benefit of early ADT initiation. However, it is clear that ADT increases risk of

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cardiometabolic morbidity and possible even mortality, especially in older and sicker men[9-12, 14-16]. In this study, we showed that clinicians delay initiation of ADT based on advanced age but not worse comorbidity, despite adjustment for tumor risk variables such as PSADT, margins status, and PSA at recurrence. These results appeared to persist in subgroups of men who received or did not receive adjuvant/salvage radition therapy, though ADT was in general started at much earlier timepoints across the board in those receiving radiation therapy. Since there is no consistently proven benefit of early ADT but known cardiometabolic harms, and the main cause of death in these populations is cardiovascular disease, we feel that timing of ADT should be more precisely prescribed based on a patient's tumor risk and comorbidity profile.

The morbidity associated with ADT has been well established in previous studies, showing higher risk of cardiometabolic morbiditiy and mortality that is potentiated in older men with comorbid disease burdens. In retrospective studies, incidence of diabetes, coronary heart disease, myocardial infarction and sudden cardiac death were all found to be increased 1.2–1.4-fold among men being treated with ADT for advanced prostate cancer [10, 11]. Furthermore, even short-term ADT increased cardiometabolic disease severity for patients with pre-existing comorbidity[10, 11]. Even more concerning are the downstream effects on cardiac morbidity and mortality. An analysis of SEER-Medicare data demonstrated a 20% increased risk of cardiovascular morbidity in men treated with ADT for at least 1 year[9]; this risk was potentiated in men with CCI scores of 1+ (vs. 0), who had 1.6-fold higher hazard of cardiovascular morbidity. Other work has shown that even 4 months of adjuvant ADT given with brachytherapy

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increases risk of cardiovascular mortality among men with known coronary artery disease resulting in heart failure or myocardial infarction[16]. We feel the substantial health risks of ADT support a more cautioned approach to timing of ADT in men with underlying cardiac comorbidities.

Whether early initiation of ADT has a benefit in terms of cancer control has not been consistently demonstrated in trials, and the bulk of the evidence suggests no benefit for older men. A pooled meta-analysis of four randomized controlled trials evaluating early (at PSA<0.2) versus delayed ADT (at higher PSA value but before metastasis) showed no difference in cancer mortality[4]. There was no difference in overall survival observed until after 10 years, favoring early ADT (OR1.5, 95%CI 1.04–2.16), but few patients survived long enough to reap this benefit. The recent TOAD trial, a randomized, non-blinded trial of immediate versus delayed ADT in men with BCR after definitive therapy (or in men unsuitable for definitive therapy), showed an overall survival benefit at 5 years favoring the immediate ADT arm (5-year overall survival 86% versus 91%, log-rank p=0.047) in the aggregate analysis[3]. However, results were not statistically significant in the BCR subgroup; cancer-specific mortality did not differ between study arms; and serious cardiac complications were higher in the immediate (9%) versus delayed (6%) arm. Moreover, in a pre-planned combined analysis with the ELAAT trial, there was no difference in all-cause mortality or cancer-specific mortality between men treated with immediate versus delayed ADT[2]. Indeed, as the authors of the latter study mention, further work is needed to identify who will benefit from early

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versus delayed ADT, and many patients will die of causes other than cancer without having a complication related to their disease[2].

Given the known harms and uncertain benefits of ADT in older men with significant comorbidity, we feel that clinicians should more strongly consider tailoring timing of ADT for BCR based on age/comorbidity and tumor risk features. In the historical literature describing natural history of PSA progression after RP, the median actuarial time from BCR to metastasis is 5 years, which has prompted some advocate withholding ADT until symptomatic disease progression appears in all patients [27]. However, we feel a more tailored approach balancing tumor risk with expected longevity shoud be considered, in order to minimize risk of treatment-related morbidity and maximize benefit. Younger men with minimal comorbidity who have higher disease risk (e.g. short PSADT) may benefit most from early initiation of ADT, since data suggest that survival benefits of immediate ADT are not realized until many years later. Conversely, older, sicker men may be best suited for delayed initiation of ADT unless high-risk tumor features (e.g. short PSADT) exist. Comparative effectiveness studies are needed to determine cutpoints for appropriate triage of ADT based on age, comorbidity and tumor risk, but it seems reasonable to withhold ADT until a higher threshold for older, sicker men who are most likely to be harmed and least likely to benefit from therapy.

Our study has some limitations. First, we did not capture details on ADT exposure (e.g. intermittent versus continuous, duration) or differentiate between ADT given as monotherapy versus adjuvant with salvage radiation. However, even short courses of

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adjuvant radiation have been associated with substantial morbidity, so we feel our endpoint to be justified[16]. Second, our cohort includes only men from the VA, which utilizes a non-fee-for-service payment model that may be less influenced by financial considerations than other payment models, though ADT is a low-cost and low-reimbursement intervention. Third, our cohort included only men who underwent radical prostatectomy as primary treatment, which will result in selection of healthier men compared with radiation or observation. Because these healthier men would be expected to have longer longevity compared with age- and comorbidity-matched peers receiving other forms of therapy, it may bias towards earlier initiation of ADT.

CONCLUSIONS

In this study, we found that men with significant comorbid disease burdens who develop BCR after radical prostatectomy often receive ADT at relatively low PSAs. Though age appears to strongly affect timing of ADT—with older men receiving ADT at slightly higher PSA values than younger men—comorbidity has little effect on timing of ADT, even among men with lower tumor risk. Since men with significant comorbidity are most likely to be harmed by ADT, we hope that these data will help to spur clinicians to delay ADT in these men unless they are at high risk for progression.

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Table 1. Sample Characteristics by Timing of ADT

	PSA <0.2 (N=131)	PSA 0.2-2.4 (N=359)	PSA 2.5-9.9 (N=166)	PSA >=10 (N=85)	At metastases (N=96)	No ADT (N=1260)	p value
Age at BCR							<0.001[2]
<60	38 (29%)	110 (31%)	27 (16%)	21 (25%)	13 (14%)	251 (20%)	
60-64	39 (30%)	100 (28%)	51 (31%)	20 (24%)	27 (28%)	284 (23%)	
65-69	36 (27%)	89 (25%)	46 (28%)	26 (31%)	36 (38%)	374 (30%)	
70-74	17 (13%)	46 (13%)	26 (16%)	15 (18%)	12 (13%)	221 (18%)	
≥75	1 (1%)	14 (4%)	16 (10%)	3 (4%)	8 (8%)	130 (10%)	
CCI at BCR							0.136[2]
0	38 (29%)	118 (33%)	72 (43%)	30 (35%)	41 (43%)	401 (32%)	
1	28 (21%)	77 (21%)	26 (16%)	16 (19%)	11 (11%)	262 (21%)	
2	15 (11%)	50 (14%)	22 (13%)	12 (14%)	15 (16%)	205 (16%)	
3	50 (38%)	114 (32%)	46 (28%)	27 (32%)	29 (30%)	392 (31%)	
Year of BCR	2013 (08-15)	2009 (04-13)	2005 (00-10)	2007 (02-11)	2008 (02-12)	2010 (03-14)	<0.001[1]
CCI at ADT							0.520[2]
0	38 (29%)	86 (24%)	35 (21%)	17 (20%)	22 (23%)	0 (0%)	
1	27 (21%)	70 (19%)	27 (16%)	15 (18%)	10 (10%)	0 (0%)	
2	14 (11%)	53 (15%)	23 (14%)	12 (14%)	11 (11%)	0 (0%)	
3	52 (40%)	150 (42%)	80 (48%)	41 (48%)	53 (55%)	1 (100%)	
Race							0.514[2]
Non-black	85 (65%)	222 (62%)	115 (69%)	52 (61%)	62 (65%)	835 (66%)	
Black	45 (35%)	136 (38%)	51 (31%)	33 (39%)	34 (35%)	421 (34%)	
Preoperative D'Amico risk group							<0.001[2]
Low	11 (9%)	47 (13%)	21 (14%)	7 (9%)	7 (8%)	323 (27%)	
Intermediate	59 (46%)	137 (39%)	56 (36%)	29 (36%)	36 (40%)	525 (44%)	
High	59 (46%)	170 (48%)	77 (50%)	44 (55%)	46 (52%)	336 (28%)	
Months from RP to BCR							<0.001[1]
Median	9.2	9.4	11.7	9.7	10.6	26.7	

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	PSA <0.2 (N=131)	PSA 0.2-2.4 (N=359)	PSA 2.5-9.9 (N=166)	PSA >=10 (N=85)	At metastases (N=96)	No ADT (N=1260)	p value
Q1, Q3	5.2, 15.9	2.5, 27.8	2.3, 32.8	2.1, 37.0	2.8, 36.0	9.7, 57.4	
Post-op grade group							<0.001[2]
1	7 (5%)	34 (10%)	22 (14%)	8 (10%)	13 (14%)	283 (24%)	
2	43 (33%)	120 (34%)	51 (32%)	28 (34%)	22 (24%)	499 (42%)	
3	33 (26%)	85 (24%)	30 (19%)	20 (24%)	21 (23%)	249 (21%)	
4	17 (13%)	48 (13%)	23 (15%)	13 (16%)	8 (9%)	93 (8%)	
5	29 (22%)	70 (20%)	31 (20%)	13 (16%)	27 (30%)	78 (6%)	
Pathological stage							<0.001[2]
T0-T2	47 (36%)	155 (43%)	76 (46%)	38 (45%)	39 (41%)	836 (66%)	
T3	71 (54%)	177 (49%)	78 (47%)	41 (48%)	50 (52%)	356 (28%)	
T4	13 (10%)	27 (8%)	12 (7%)	6 (7%)	7 (7%)	68 (5%)	
Positive surgical margins	81 (62%)	214 (60%)	89 (54%)	37 (44%)	52 (56%)	688 (55%)	0.086[2]
Extracapsular extension	62 (47%)	158 (45%)	73 (45%)	37 (46%)	45 (48%)	335 (27%)	<0.001[2]
Seminal vesicle invasion	44 (34%)	106 (30%)	48 (29%)	21 (25%)	33 (35%)	145 (12%)	<0.001[2]
Lymph node involvement							<0.001[2]
No	91 (69%)	239 (67%)	109 (66%)	61 (72%)	77 (80%)	846 (67%)	
Yes	15 (11%)	51 (14%)	15 (9%)	10 (12%)	5 (5%)	20 (2%)	
Not done	25 (19%)	69 (19%)	42 (25%)	14 (16%)	14 (15%)	394 (31%)	
PSA at recurrence (ng/ml)	0.1 (0.1-0.2)	0.3 (0.2-0.5)	0.5 (0.3-1.5)	0.6 (0.3-4.7)	0.4 (0.2-1.1)	0.2 (0.2-0.3)	<0.001[1]
PSADT at recurrence (mo)							<0.001[2]
≥9	3 (2%)	99 (28%)	63 (38%)	27 (32%)	26 (27%)	606 (27%)	
<9	1 (1%)	60 (17%)	47 (28%)	26 (31%)	29 (31%)	106 (30%)	
Not calculable	127 (97%)	200 (56%)	56 (34%)	32 (38%)	41 (38%)	548 (43%)	
Salvage XRT	109 (83%)	262 (73%)	100 (60%)	34 (40%)	32 (33%)	710 (56%)	<0.001[2]

[1]Kruskal Wallis [2]Chi-Square
Continuous variables show median (25th percentile, 75th percentile)

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Table 2: **Cox Multivariable Regression Association Between Covariates and Timing of ADT***

	All patients (N=2,097)			No XRT (N=850)			XRT (N=1,247)		
	HR	**95% CI**	**p**	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
CCI			0.25			0.70			0.11
0	Ref.			Ref.			Ref.		
1	0.89	0.73-1.08		1.10	0.76-1.57		0.81	0.63-1.03	
2	0.90	0.72-1.13		1.19	0.81-1.75		0.75	0.57-0.99	
3+	0.83	0.70-1.00		0.94	0.67-1.33		0.81	0.65-1.01	
Age			0.03			0.16			0.21
<60	Ref.			Ref.			Ref.		
60-64	0.89	9.73-1.08		0.68	0.46-1.00		0.98	0.78-1.22	
65-69	0.73	0.60-0.89		0.67	0.46-0.98		0.78	0.61-0.99	
70-74	0.84	0.67-1.07		0.90	0.61-1.33		0.82	0.59-1.12	
≥74	0.73	0.52-1.04		0.72	0.45-1.15		0.88	0.47-1.66	

* Higher hazard ratio indicates association with lower PSA at initiation of ADT; Lower hazard ratio indicates association with higher PSA at initiation of ADT
Model is adjusted for year of BCR, PSA doubling time, salvage radiation, surgical center, PSA at surgery, PSA at recurrence, clinical stage, pathological stage, and positive lymph nodes

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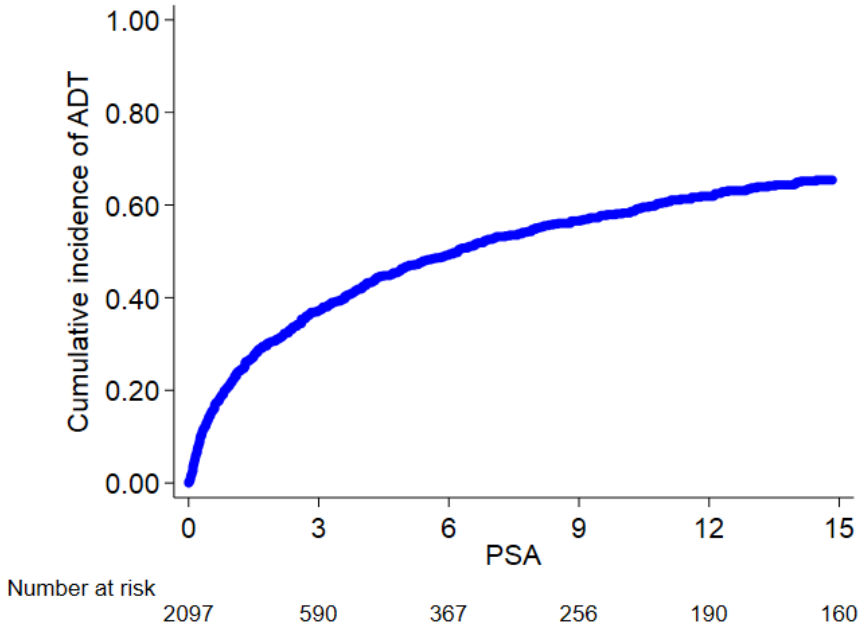
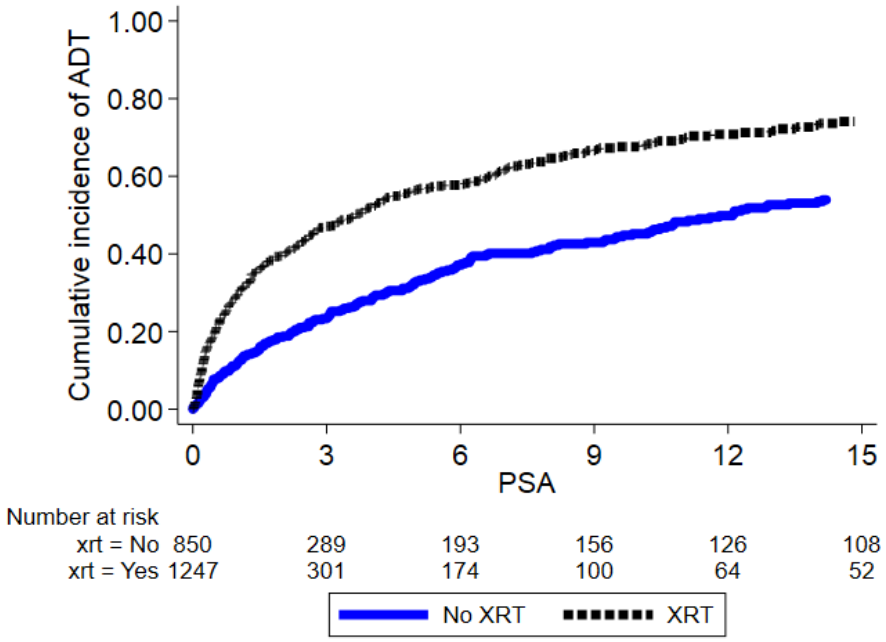
Figure 1. Cumulative Incidence of ADT Utilization according to PSA* (A) across All Patients and (B) Stratified by Receipt of Radiation Therapy

(A) All Patients



(B) Stratified by Receipt of Radiation Therapy



* Highest PSA used as censor time for patients who did not receive ADT

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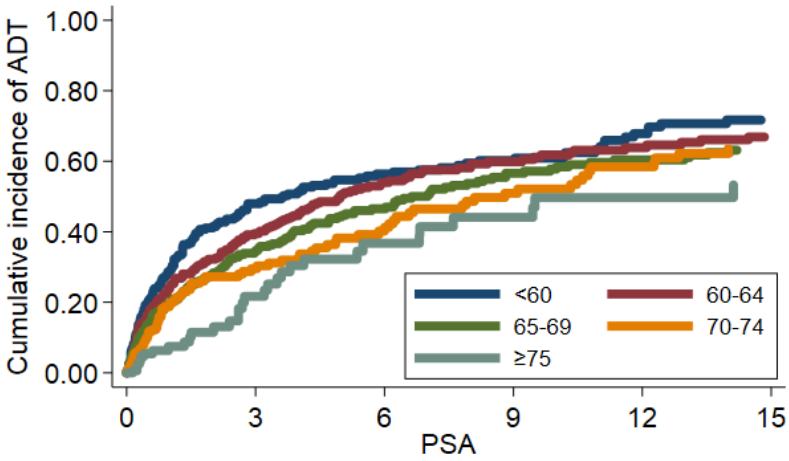
Figure 2. Cumulative Incidence of ADT Utilization according to PSA Stratified by Age at Biochemical Recurrence

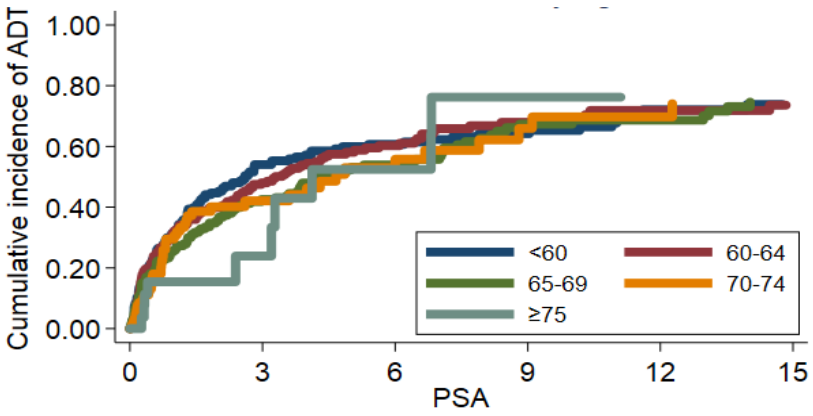
(A) All Patients



Number at risk

<60	460	115	77	57	34	27
60-64	521	170	94	64	48	42
65-69	607	170	110	75	59	51
70-74	337	90	59	40	33	27
≥75	172	45	27	20	16	13

(B) Received Radiation Therapy



Number at risk

<60	347	75	50	34	18	14
60-64	344	100	51	27	17	14
65-69	374	88	52	28	21	17
70-74	149	30	17	9	7	6
≥75	33	8	4	2	1	1

(C) Did not Receive Radiation Therapy

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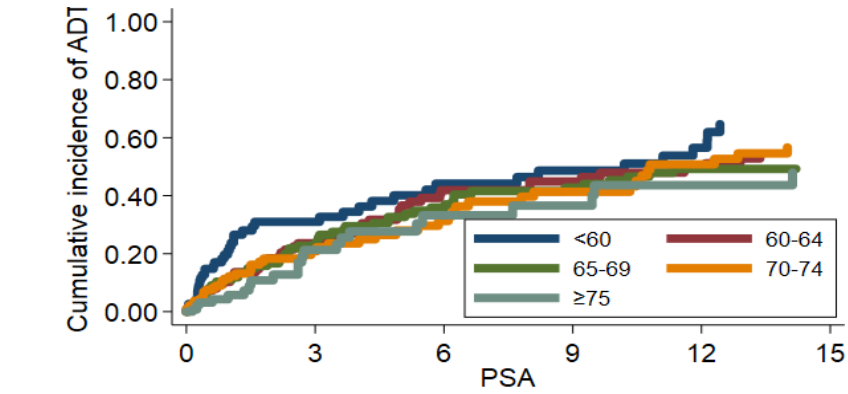

Number at risk						
<60	113	40	27	23	16	13
60-64	177	70	43	37	31	28
65-69	233	82	58	47	38	34
70-74	188	60	42	31	26	21
≥75	139	37	23	18	15	12

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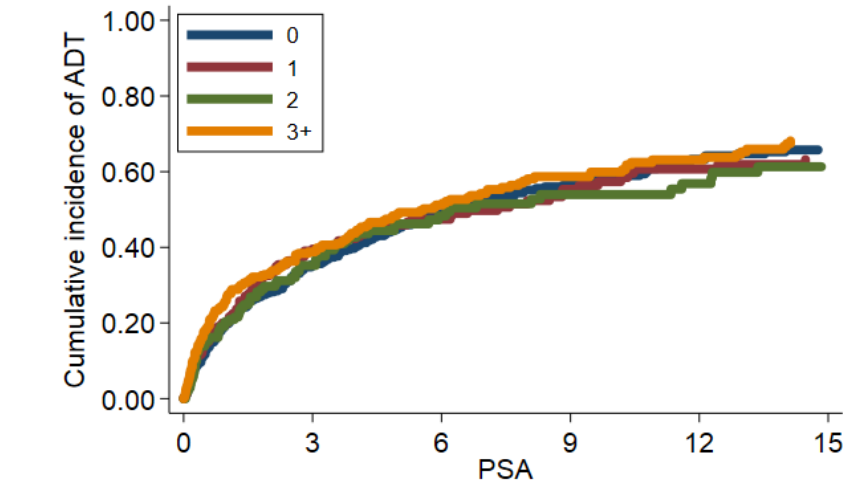
Figure 3. Cumulative Incidence of ADT Utilization according to PSA Stratified by Charlson Comorbidity Index at Biochemical Recurrence

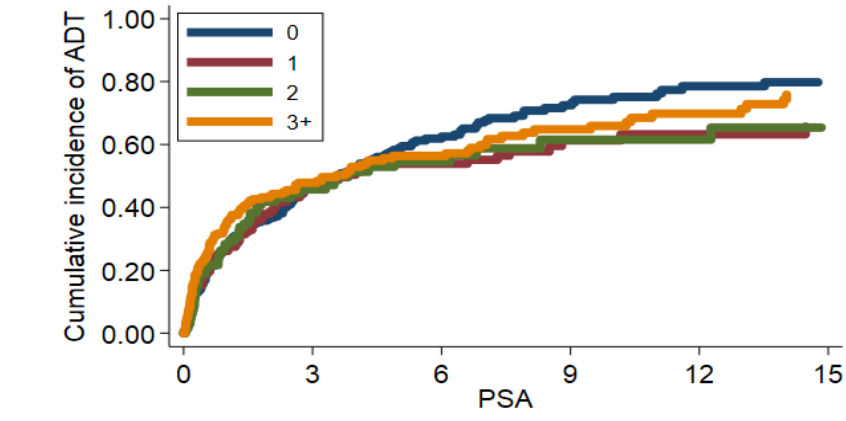
(A) All Patients



Number at risk

0	700	228	149	104	75	63
1	420	115	68	44	33	28
2	319	79	50	38	30	25
3+	658	168	100	70	52	44

(B) Received Radiation Therapy



Number at risk

0	408	107	60	32	18	14
1	255	67	38	21	16	14
2	199	40	22	14	10	8
3+	385	87	54	33	20	16

(C) Did not Receive Radiation Therapy

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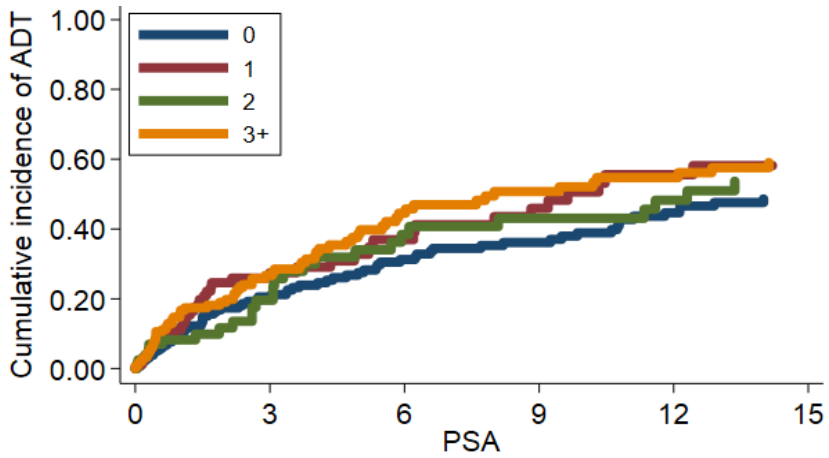

Number at risk

0	292	121	89	72	57	49
1	165	48	30	23	17	14
2	120	39	28	24	20	17
3+	273	81	46	37	32	28

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Competing Risks of Mortality among Men with Biochemical Recurrence after Radical Prostatectomy

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Purpose: Men with biochemical recurrence after radical prostatectomy need information on competing risks of mortality to inform prognosis and guide treatment. We quantified the risk of prostate cancer metastasis and mortality, and other cause mortality across key clinical predictors.

Materials and Methods: We analyzed 1,225 men with biochemical recurrence after radical prostatectomy from 2001 to 2017 in the VA SEARCH database. Multivariable competing risks regression was used to identify predictors and quantify cumulative incidence of metastasis, prostate cancer specific mortality and other cause mortality. Recursive partitioning analysis was used to identify optimum variable cut points for prediction of prostate cancer specific mortality and other cause mortality.

Results: During a median followup of 5.6 years after biochemical recurrence (IQR 2.7–9.1), 243 (20) men died of other causes and 68 (6) died of prostate cancer. Multivariable competing risks regression showed that high D'Amico tumor risk and prostate specific antigen doubling time at biochemical recurrence less than 9 months were associated with metastasis and prostate cancer specific mortality ($p \leq 0.001$). Ten-year prostate cancer specific mortality was 14 and 9 for those with high risk tumors and prostate specific antigen doubling time less than 9 months, respectively. Advanced age and worse comorbidity were associated with other cause mortality ($p \leq 0.001$). Ten-year other cause mortality was higher among men 70 years old or older with any Charlson comorbidity (1–3) (40 to 49) compared to those with none (20). Recursive partitioning analysis identified optimal variable cut points for prediction of prostate cancer specific mortality and other cause mortality, with 10-year prostate cancer specific mortality ranging from 3 to 59 and 10-year other cause mortality ranging from 17 to 50 across risk subgroups.

Conclusions: Among men with biochemical recurrence after radical prostatectomy, there is significant heterogeneity in prognosis that can be explained by available clinical variables. Men in their 70s with any major comorbidity are 2 to 10 times more likely to die of other causes than of prostate cancer.

Key Words: comorbidity, age groups, prostatic neoplasms, risk, survival

Abbreviations and Acronyms

ADT androgen deprivation therapy
BCR biochemical recurrence
CCI Charlson comorbidity index
OCM other cause mortality
PC prostate cancer
PCSM prostate cancer specific mortality
PSA prostate specific antigen
PSADT prostate specific antigen doubling time
RP radical prostatectomy
VA Veterans Affairs
XRT radiation therapy

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Editor s Note: This article is the third of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 626 and 627.

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DESPITE biochemical recurrence after radical prostatectomy being exceedingly common, with an annual U.S. incidence of approximately 29,000 cases,[1–3] there is a paucity of risk stratification data to inform prognosis and treatment strategies in these men. Previous data have shown that men with BCR are unlikely to die of their disease, with 5, 10 and 15-year cancer specific mortality rates of only 3 , 11 , and 21 , respectively.[4] However, rates of prostate cancer metastasis and prostate cancer specific mortality by key clinical predictors as well as information on the competing risk of other cause mortality are lacking. Improved risk stratification for these competing risks can help men with BCR better understand their prognosis and may identify groups that are more or less likely to benefit from intensive treatment strategies.

Competing risks information is particularly relevant to the question of timing of androgen deprivation therapy in men with BCR after surgery. Immediate initiation of ADT after BCR (as opposed to waiting until higher PSA or clinical progression) has not been consistently shown to improve outcomes,[5–8] and meta-analysis data suggest that benefits may be delayed until 10 years after treatment.[9] Because men with BCR after surgery tend to be older (given the time lag after radical prostatectomy) and have comorbidity burdens, they may not have sufficient longevity to reap survival benefits of early ADT, which is supported by post hoc analysis of randomized trials comparing early vs delayed ADT.[10] Moreover, the potential morbidity of ADT, including elevated risk of cardiometabolic disease and mortality, in these men is substantially higher than in younger, healthier men.[11,12] Hence, understanding who is most likely to live long enough to be harmed by their cancer is a critical determinant that should be considered when planning treatment.

We determined the key predictors of long-term prostate cancer metastasis, PCSM and OCM among men with BCR after RP. We then quantified long-term metastasis and mortality rates across these key predictor variables. To do this, we used the SEARCH database, which includes men who underwent RP across 8 VA medical centers.[13] This database is uniquely suited to answer this question since SEER (Surveillance, Epidemiology, and End Results)-Medicare and the National Cancer Database lack key data elements (eg longitudinal PSA, PSADT at BCR, detailed stage and grade data, cause of death) that prohibit characterization of primary predictors or outcomes. We hypothesized that subgroups could be identified that have high risk of OCM and low risk of cancer mortality (and vice versa). These data could be used to inform prognosis and treatment in men with BCR after RP, and also permit further study of timing of ADT in post hoc analyses of randomized controlled trials comparing early vs delayed ADT.

MATERIALS AND METHODS

Study Population

The SEARCH database includes men with prostate cancer treated with RP from 1988 to 2017 across 8 VA medical centers (7,811).[13] We identified men with BCR after RP (defined as 1 PSA greater than 0.2 ng/ml, 2 PSAs of 0.2 ng/ml, or secondary treatment for a rising PSA)[14] between 2001 and 2018 (year range based on availability of comorbidity data) (sample size 1,481). We excluded men with pathological node positive prostate cancer (91), and those with missing clinical stage (8), race (12), margin status (9), pathological grade group (25), preoperative D'Amico risk category (108) or PSA at recurrence (3). Our final study cohort included 1,225 men (supplementary fig. 1, https://www.jurology.com). The study received IRB approval (IRB No. Pro00044354).

Variables

Predictor Variables Age at BCR (less than 65, 65 to 69, 70 years old or older) was obtained by review of the electronic medical record. Deyo-Charlson comorbidity index score at BCR (0, 1, 2, 3) was calculated using inpatient and outpatient claims.[15] D'Amico tumor risk,[16] clinical stage, pathological characteristics (grade, stage, surgical margin, extracapsular extension, seminal vesicle invasion, lymph node involvement), PSA doubling time at BCR[17] and receipt of adjuvant/salvage XRT were ascertained by review of the electronic medical record. Sociodemographic information was also collected, including year of BCR and race.

Primary Outcomes Baseline for all survival outcomes was the date of BCR. Cause of death was defined as PCSM or OCM based on electronic medical record chart review. Men were considered to have died of PC if they had progressive prostate cancer metastases resistant to castration and death without another probable cause, also taking into account if they had renal failure with ureteral obstruction and hydronephrosis, had locally advanced disease and/or had entered hospice for PC. Nondeceased patients were followed to date of last contact with the VA Health System.

Statistical Analysis

Baseline characteristics stratified by Charlson comorbidity index were compared using chi-squared tests for categorical variables and Kruskal-Wallis tests for continuous variables.

Competing risks models were used to estimate subhazard ratios for OCM and PCSM, with the other outcome acting as the competing risk. The analysis was also carried out for the outcome of metastasis, with OCM as the competing risk. Variables were selected using backward stepwise selection with alpha 0.05 for entry and alpha 0.10 for removal. Candidate variables included age at BCR, Charlson comorbidity index at BCR, PSA at recurrence (log transformed), PSADT at BCR, pathological grade group, preoperative D'Amico risk group, surgical margin status, race, salvage radiation (time dependent), surgical center and year of BCR. Interactions between age and comorbidity were

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tested and were not significant for any outcome. Cumulative incidence curves from the multivariable models were graphed.

We then performed recursive partitioning based on our survival models to empirically sort patients into groups of similar risk. Recursive partitioning is a statistical method that optimizes risk stratification by empirically identifying optimal variables and variable cut points, ultimately creating a decision tree with terminal branches representing groups of patients with similar risk. The minimum criterion for dividing a group was p ≤0.10. Kaplan-Meier plots were created to show the differences in survival between the risk groups.

Statistical analyses were performed using Stata® 15.0 and R v3.5.3 (R Foundation for Statistical Computing, Vienna, Austria). A double-sided p 0.05 denoted statistical significance.

RESULTS

Median followup after BCR was 5.6 years (IQR 2.7–9.1). Of the 1,225 men in our sample 243 (20) died of other causes and 68 (6) died of prostate cancer. Median age at BCR across our sample was 62 years (IQR 58–66). Men in our sample tended to have substantial comorbidity burdens, with 50 of patients having Charlson scores of 2 or greater. Those with worse comorbidity burdens tended to be treated less often with salvage XRT and tended to have longer PSADT (supplementary table 1, https://www.jurology.com).

Multivariable competing risks regression with backward stepwise selection identified variables that were significantly associated with PCSM, metastasis and OCM (see table). Variables that were significantly associated with higher risk of metastasis and PCSM were higher preoperative D'Amico tumor risk, higher PSA at BCR and shorter PSADT (all p ≤0.001). Variables significantly associated with higher risk of OCM were advanced age at BCR (p 0.001), CCI at BCR (p 0.001), earlier year of BCR (p 0.001), surgery center (p 0.01) and no use of salvage XRT (p 0.001).

Multivariable competing risks regression models including all statistically significant variables were then used to project cumulative incidence estimates for PCSM, metastasis (fig. 1; parts *A* and *B* of supplementary table 2, https://www.jurology.com), and OCM (fig. 2, part *C* of supplementary table 2, https://www.jurology.com) across subgroups of key actionable predictor variables (preoperative D'Amico tumor risk and PSADT at BCR for cancer metastasis and mortality; age and CCI score for OCM). Risk of cancer metastasis and mortality increased in stepwise fashion with higher tumor risk and lower PSADT at BCR. Cumulative incidence of prostate cancer metastasis and mortality for men with PSADT at BCR less than 9 months were 16 and 9 at 10 years after BCR, respectively (supplementary table 2, https://www.jurology.com). Cumulative incidence of OCM increased with age and comorbidity burden. However, of note, 10-year OCM was substantially higher among men 70 years old or older with CCI 1 (45), 2 (40) or 3 (49) compared to those with CCI 0 (20). Simultaneous depictions of OCM and PCSM by age and CCI are shown in supplementary figure 2 (https://www.jurology.com).

Recursive partitioning analysis was used to empirically identify optimal variable risk stratification cut points for prediction of PCSM (supplementary fig. 3, *A*, https://www.jurology.com) and OCM (supplementary fig. 3, *B*, https://www.jurology.com). The branchpoints identified to

Multivariable competing risks models predicting time from BCR to death from prostate cancer prostate cancer metastasis and death from other causes

	SHR	95 CI	p Value
	Death from PC		
Salvage radiation	0.45	0.28–0.73	0.001
D'Amico risk group:			0.001
Low	Reference		
Intermediate	1.62	0.68–3.81	
High	4.10	1.87–9.01	
PSA at BCR	1.61	1.38–1.87	0.001
PSADT (mos) at BCR:			0.001
9 or More	Reference		
Less than 9	2.46	1.22–4.96	
Unknown	3.41	1.90–6.12	
	PC metastasis		
D'Amico risk group:			0.001
Low	Reference		
Intermediate	2.27	1.18–4.36	
High	3.35	1.73–6.48	
PSA at recurrence	1.56	1.33–1.82	0.001
PSADT (mos) at BCR:			0.001
9 or More	Reference		
Less than 9	2.28	1.41–3.70	
Unknown	1.97	1.29–3.03	
Postop grade group:			0.013
1	Reference		
2	1.46	0.72–2.96	
3	1.87	0.89–3.94	
4–5	2.74	1.31–5.71	
	Death from other causes		
Age at BCR:			0.001
Younger than 65	Reference		
65–69	1.30	0.92–1.82	
70 or Older	2.08	1.52–2.83	
CCI at BCR:			0.001
0	Reference		
1	1.61	1.08–2.40	
2	1.59	1.03–2.45	
3+	2.40	1.68–3.44	
Yr of BCR	0.92	0.89–0.96	0.001
Surgery center:			0.010
West LA	Reference		
Palo Alto	0.66	0.39–1.10	
San Francisco	0.50	0.26–0.99	
Augusta	0.76	0.46–1.28	
Durham	1.32	0.87–1.98	
San Diego	0.93	0.62–1.40	
Asheville	1.39	0.91–2.12	
Portland	0.63	0.32–1.24	
Salvage XRT	0.42	0.32–0.54	0.001

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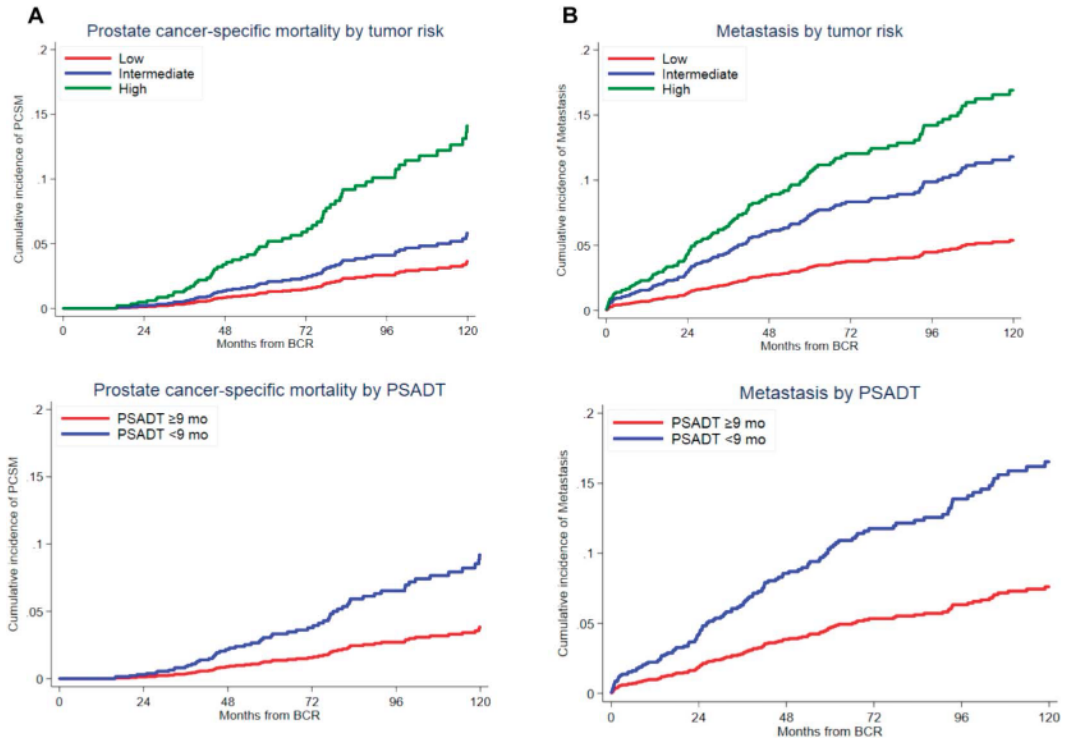

Figure 1. Cumulative incidence of PCSM (*A*) and metastasis (*B*) by PSADT at BCR and D Amico preoperative risk category

predict PCSM were PSA at recurrence (less than 10 vs 10 ng/ml or greater), D'Amico tumor risk (low/intermediate vs high) and PSADT (less than 9 vs 9 or more months) (supplementary fig. 3, *A*, https://www.jurology.com). Cumulative incidence curves noting PCSM across these subgroups showed that

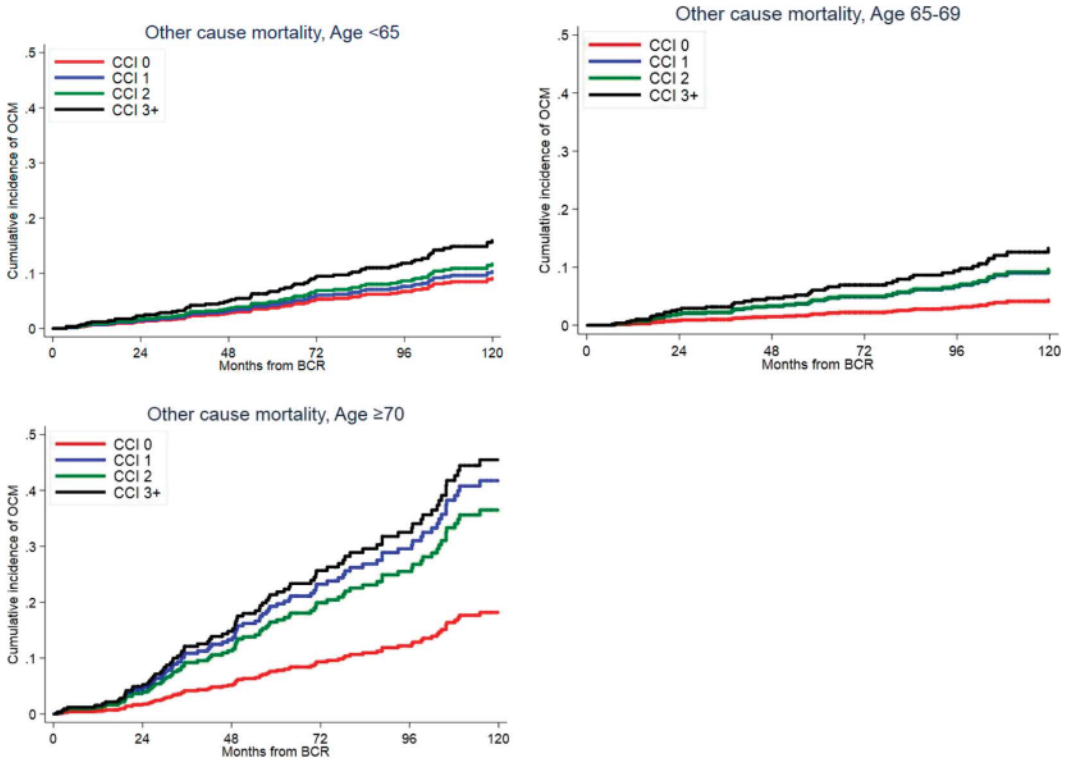

Figure 2. Cumulative incidence of other cause mortality by age and CCI

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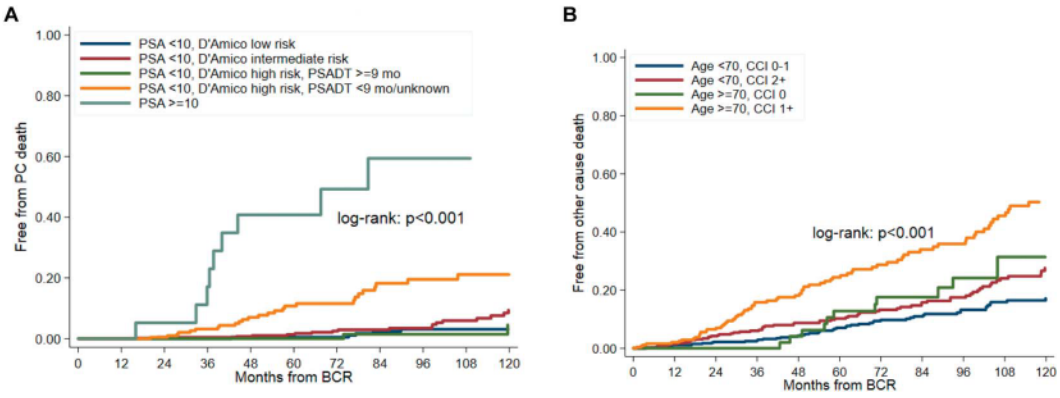

Figure 3. Cumulative incidence curves based on recursive partitioning subgroups for PCSM (*A*) and OCM (*B*)

men with PSA at BCR 10 ng/ml or greater, D'Amico high risk and PSADT less than 9 months (or unknown) had a 10-year PCSM of 21 (fig. 3, *A*). Conversely, branchpoints to predict OCM were age at BCR (less than 70 vs 70 years old or older) and CCI at BCR (for those less than 70 years old, CCI less than 2 vs 2 or greater; for those 70 years old or older, CCI 0 vs 1 or more). Kaplan-Meier curves noting OCM across these subgroups showed that men 70 years old or older with any Charlson comorbidities had a 10-year OCM of 50 (fig. 3, *B*).

DISCUSSION

This study quantifies the competing risks of PCSM, OCM and metastasis among men with BCR after RP according to their main clinical predictors. Long-term cumulative incidence of prostate cancer metastasis and mortality were low even among those at highest risk. For example, 10-year prostate cancer metastasis and PCSM were 16 and 14 , respectively, among those with high preoperative D'Amico tumor risk. Conversely, the competing 10-year risk of OCM was also low (less than 20) for the majority of patients, except for those 70 years old or older with any degree of comorbidity (45 , 40 and 49 for those with CCI 1, 2 and 3 , respectively). We empirically validated these risk stratifications with recursive partitioning analysis, identifying subgroups at highest and lowest risk for PCSM (ie men with high preoperative D'Amico tumor risk and PSADT less than 9 months or unknown) and OCM (ie men 70 years old or older with CCI scores of 1 or higher). Defining long-term competing risks estimates in these men is critical to inform discussion of prognosis, since they may have the misconception that they are highly likely to die of their disease, especially if they have adverse disease risk characteristics. This information is also essential to inform comparative effectiveness studies in this population, as patients at high risk for OCM and low risk for PCSM may be more likely to benefit from delayed ADT or derive no benefit from intensified androgen blockade.

While it is already known that few men with BCR after RP actually die of prostate cancer, our study provides greater detail regarding risk stratification of cancer metastasis and mortality outcomes across predictor variables, allowing for more precise estimates of prognosis for an individual patient. In a previously published cohort of 225 U.S. veterans with PC who underwent RP, the 5, 10 and 15-year cumulative incidence of BCR after prostatectomy was 34 , 37 and 37 , but the cumulative incidence of PCSM among those with recurrence was only 3 , 11 and 21 at 5, 10 and 15 years, respectively.[4] In our study quantification of risk of PCSM across PSADT at BCR and preoperative D'Amico tumor risk permits a more personalized approach to prognosis assessment. For example, the 10-year cumulative incidence of PCSM ranges from 3.6 to 14.1 depending on D'Amico tumor risk and 3.8 to 9.2 based on PSADT at BCR.

Because prostate cancer affects mainly older men, assessment of prognosis and treatment decisions must also consider the risk of OCM in addition to risk of death from prostate cancer. In our study the competing risk of OCM was appreciable in men 70 years old or older with any degree of comorbidity, approaching 40 to 50 at 10 years. This information is relevant for timing of androgen deprivation therapy in these men, because survival benefits from immediate initiation of ADT have been shown to develop over a protracted time horizon (ie 10 years) and may not accrue during their lifetime.[9] Furthermore, ADT may incur higher risks of major side effects including cardiovascular morbidity and mortality[11,12] in these men compared with their younger and healthier peers.[18,19] In the PSA era physicians have begun initiating ADT earlier in the disease course (ie immediately at the time of BCR), and we have found in the SEARCH

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population that 50 of men 70 years old or older receive ADT at PSA less than 8.8 ng/ml (unpublished data). Based on their high risk of OCM, the modest likelihood of treatment benefit and the high likelihood of treatment morbidity, these men may be better suited to starting ADT later.

Identification of subgroups of men who are less likely to die of prostate cancer and more likely to die of other causes during a 10-year period (and vice versa) may help to facilitate comparative effectiveness studies of ADT timing in men with BCR as benefits of early therapy appear to be delayed this long. A pooled meta-analysis of 4 randomized controlled trials evaluating early (at PSA less than 0.2 ng/ml) vs delayed ADT (at higher PSA value but before metastasis) in men with BCR showed that overall survival benefits of early ADT were not observed until after 10 years (OR 1.5, 95 CI 1.04−2.16), but few patients survived long enough to reap this benefit.[9] Moreover, a recent post hoc analysis of 206 men on a clinical trial who had BCR after definitive radiation therapy, BCR was not linked with an increased risk of PCSM in patients with moderate or severe comorbidity, in contrast to men with no or mild comorbidity in whom BCR was linked with PC death.[10] It is possible that post hoc analyses of existing randomized controlled trials comparing long-term mortality associated with early vs delayed ADT may show differential effects in those least likely to benefit (ie men older than 70 years with CCI scores of 1 or higher and PSADT 9 or more months with preoperative low/intermediate D'Amico risk) and those most likely to benefit (ie those younger than 70 or older than 70 with no major comorbidities and PSADT less than 9 months with high preoperative D'Amico risk) based on competing risks profiles.

There are several limitations of our analysis. Survival data from the VA may not directly translate to nonVA settings, given differences in sociodemographics and comorbidity burden. However, prior work comparing survival outcomes in the VA with SEER-Medicare populations has shown little difference.[20,21] In addition, long-term survival may be improved now compared with 2001 to 2018, as a number of novel therapeutics (secondary androgen axis inhibition, early chemotherapy, immunotherapeutics, radiopharmaceuticals) that increase survival have since emerged. Survival estimates may not be generalizable to populations who received other forms of definitive treatment (ie radiation therapy). Finally, there was no set protocol for PSA surveillance after surgery, which may affect uniformity of this variable.

CONCLUSIONS

This study quantifies the long-term competing risks of prostate cancer metastasis and mortality and OCM in men with BCR after RP across key clinical predictors. We also empirically identified optimal risk stratification cut points to define subgroups of men who are most likely to die of other causes and, conversely, prostate cancer. This information improves precision of prognosis for men with BCR after RP and allows for individualized prediction of metastasis and mortality across readily available clinical variables. Importantly, it will also inform further study of efficacy of early vs delayed ADT in men who may be more or less likely to benefit from these therapeutic approaches. We believe that older men with comorbidity burden who are currently receiving early ADT may benefit from a delayed approach, given the protracted time course of survival benefit of early ADT and its immediate morbidity.

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Appendix 3:
Aim 3 Tables and Figure

Table 1: Patient Characteristics of Study Cohort by Early ADT Status

Patient Characteristics by Early ADT Status			
	PSA ≤ 2.5 (N=336)	PSA > 2.5 or No ADT (N=1049)	Standardized Differences, %
Age at recurrence			-32.7
Median	63	65	
Q1, Q3	59, 67	61, 70	
Race			8.2
Non-black	213 (63%)	706 (67%)	
Black	123 (37%)	343 (33%)	
Year of recurrence			-4.0
Median	2010	2010	
Q1, Q3	2006, 2014	2006, 2014	
PSA at recurrence			-17.6
Median	0.3	0.3	
Q1, Q3	0.2, 0.6	0.2, 0.5	
PCCI at recurrence			11.8
≤ 4	206 (61%)	582 (55%)	
≥ 5	130 (39%)	467 (45%)	
D'Amico Risk			28.3
Low/Intermediate risk	171 (51%)	679 (65%)	
High risk	165 (49%)	370 (35%)	
XRT			-52.5
No	92 (27%)	548 (52%)	
Yes	244 (73%)	501 (48%)	
Follow-up from recurrence (in months)			19.5
Median	72.9	64.2	
Q1, Q3	38.0, 121.9	30.0, 105.8	

Table 2: Patient Characteristics of Early ADT Patients and 5 Matched Controls

Patient Characteristics of Early ADT Patients and 5 Matched Controls

	Early ADT Patient (N=336)	Matched Control (N=1,680)	Standardized Differences, %
Age at recurrence			-23.9
Median	63	65	
Q1, Q3	59, 67	60, 69	
Race			8.3
Non-black	213 (63%)	1131 (67%)	
Black	123 (37%)	549 (33%)	
Year of recurrence			1.4
Median	2010	2010	
Q1, Q3	2006, 2014	2006, 2014	
PSA at recurrence			-3.4
Median	0.3	0.3	
Q1, Q3	0.2, 0.6	0.2, 0.4	
PCCI at recurrence			0
<=4	206 (61%)	1030 (61%)	
>=5	130 (39%)	650 (39%)	
D'Amico Risk			0
Low/Intermediate risk	171 (51%)	855 (51%)	
High risk	165 (49%)	825 (49%)	
XRT			-31.3
No	92 (27%)	707 (42%)	
Yes	244 (73%)	973 (58%)	
Follow-up from start of ADT or matched PSA			13.5
Median	58.4	42.1	
Q1, Q3	27.7, 108.7	14.1, 94.0	

** 796 unique patients*

Table 3: Sequential Stratification Stratified Cox Model, 5 matches per early ADT patient

			Univariable			Multivariable		
	#Deaths/# Early ADT	**#Deaths/ #Total**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**
All	74/336	280/2016	1.26	(0.93, 1.71)	0.14	1.49	(1.07, 2.08)	0.018
PCCI at BCR								
≤ 4	42/206	138/1236	1.40	(0.92, 2.10)	0.11	1.72	(1.11, 2.67)	0.015
≥ 5	32/130	142/780	1.13	(0.72, 1.77)	0.60	1.28	(0.80, 2.08)	0.31
D'Amico Risk at dx								
Low/Intermediate	41/171	160/1026	1.24	(0.83, 1.84)	0.30	1.49	(0.99, 2.26)	0.058
High	33/165	120/990	1.29	(0.81, 2.07)	0.29	1.62	(0.93, 2.82)	0.090

Patients matched on PCCI, D'Amico Risk, Date of BCR +/- 2 years, PSA +/- 0.5 ng/mL

Multivariable models adjusted for race (black vs other), log PSA at BCR, Radiation, and time from Recurrence to ADT (early ADT patient)/Recurrence to PSA date (matched patients)

Figure 1: Consort Diagram

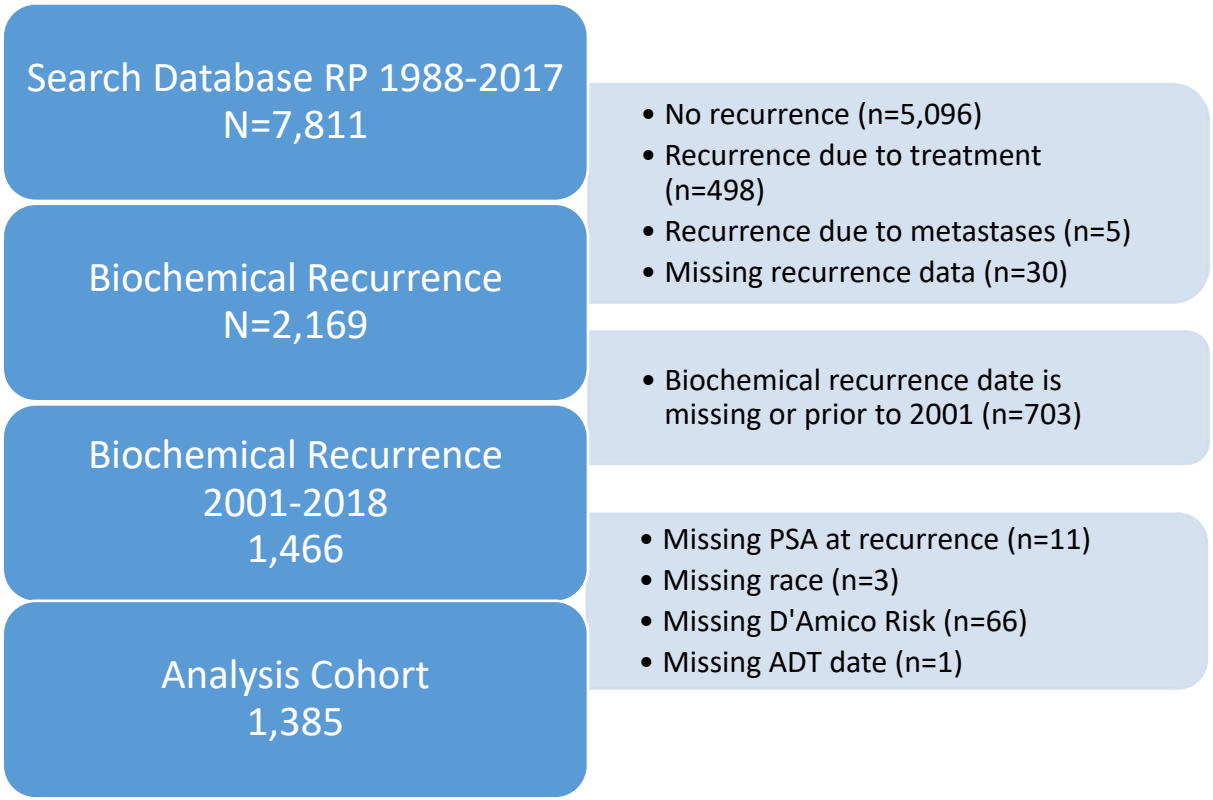
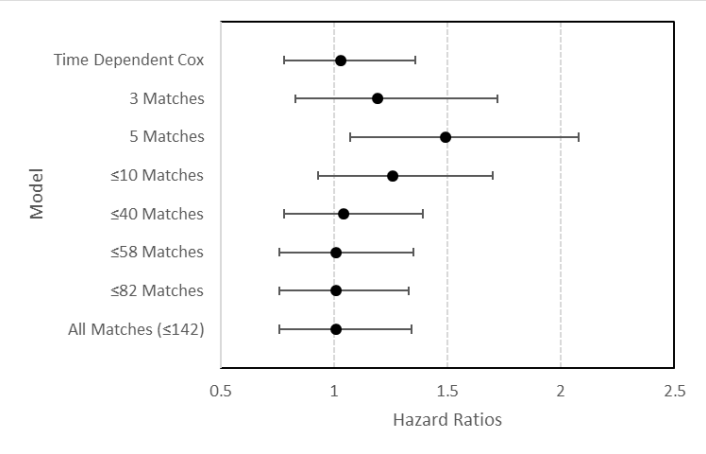


Figure 2: Strata Size vs. Magnitude and Precision of Estimates



	% of matches that are repeats	HR	95% CI
Time Dependent Cox	-	1.03	(0.78, 1.36)
3 Matches	40%	1.19	(0.83, 1.72)
5 Matches	53%	1.49	(1.07, 2.08)
≤10 Matches	69%	1.26	(0.93, 1.70)
≤40 Matches	89%	1.04	(0.78, 1.39)
≤58 Matches	92%	1.01	(0.76, 1.35)
≤82 Matches	93%	1.01	(0.76, 1.33)
All Matches (≤142)	94%	1.01	(0.76, 1.34)

Supplementary Table 1a: Patient Characteristics of Early ADT Patients and 3 Matched Controls

Patient Characteristics of Early ADT Patients and 3 Matched Controls

	Early ADT Patient (N=336)	Matched Control (N=1,008)	Standardized Differences, %
Age at recurrence			-22.6
Median	63	65	
Q1, Q3	59, 67	60, 69	
Race			5.8
Non-black	213 (63%)	667 (66%)	
Black	123 (37%)	341 (34%)	
Year of recurrence			2.2
Median	2010	2010	
Q1, Q3	2006, 2014	2005, 2014	
PSA at recurrence			1.8
Median	0.3	0.3	
Q1, Q3	0.2, 0.6	0.2, 0.4	
PCCI at recurrence			0
<=4	206 (61%)	618 (61%)	
>=5	130 (39%)	390 (39%)	
D'Amico Risk			0
Low/Intermediate risk	171 (51%)	513 (51%)	
High risk	165 (49%)	495 (49%)	
XRT			-27.9
No	92 (27%)	408 (40%)	
Yes	244 (73%)	600 (60%)	
Follow-up from start of ADT or matched PSA			16.6
Median	58.4	40.0	
Q1, Q3	27.7, 108.7	13.6, 93.3	

Suplementary Table 1b: Patient Characteristics of Early ADT Patients and up to 10 Matched Controls

Patient Characteristics of Early ADT Patients and up to 10 Matched Controls

	Early ADT Patient (N=336)	Matched Control (N=3,357)	Standardized Differences, %
Age at recurrence			-26.7
Median	63	65	
Q1, Q3	59, 67	61, 69	
Race			6.8
Non-black	213 (63%)	2237 (67%)	
Black	123 (37%)	1120 (33%)	
Year of recurrence			0.9
Median	2010	2010	
Q1, Q3	2006, 2014	2006, 2014	
PSA at recurrence			-2.8
Median	0.3	0.3	
Q1, Q3	0.2, 0.6	0.2, 0.4	
PCCI at recurrence			0.07
<=4	206 (61%)	2057 (61%)	
>=5	130 (39%)	1300 (39%)	
D'Amico Risk			0.09
Low/Intermediate risk	171 (51%)	1710 (51%)	
High risk	165 (49%)	1647 (49%)	
XRT			-33.9
No	92 (27%)	1455 (43%)	
Yes	244 (73%)	1902 (57%)	
Follow-up from start of ADT or matched PSA			13.8
Median	58.4	42.1	
Q1, Q3	27.7, 108.7	13.9, 93.1	

Supplementary Table 1c: Patient Characteristics of Early ADT Patients and up to 40 Matched Controls

Patient Characteristics of Early ADT Patients and up to 40 Matched Controls

	Early ADT Patient (N=336)	Matched Control (N=12,522)	Standardized Differences, %
Age at recurrence			-26.5
Median	63	65	
Q1, Q3	59, 67	60, 69	
Race			8.2
Non-black	213 (63%)	8428 (67%)	
Black	123 (37%)	4094 (33%)	
Year of recurrence			-4.6
Median	2010	2010	
Q1, Q3	2006, 2014	2006, 2014	
PSA at recurrence			-1.5
Median	0.3	0.3	
Q1, Q3	0.2, 0.6	0.2, 0.4	
PCCI at recurrence			-1.8
<=4	206 (61%)	7784 (62%)	
>=5	130 (39%)	4738 (38%)	
D'Amico Risk			5.0
Low/Intermediate risk	171 (51%)	6688 (53%)	
High risk	165 (49%)	5834 (47%)	
XRT			-34.7
No	92 (27%)	5480 (44%)	
Yes	244 (73%)	7042 (56%)	
Follow-up from start of ADT or matched PSA			22.2
Median	58.4	36.1	
Q1, Q3	27.7, 108.7	12.0, 84.3	

Supplementary Table 1d: Patient Characteristics of Early ADT Patients and up to 58 Matched Controls

Patient Characteristics of Early ADT Patients and up to 58 Matched Controls

	Early ADT Patient (N=336)	Matched Control (N=16,314)	Standardized Differences, %
Age at recurrence			-24.8
Median	63	65	
Q1, Q3	59, 67	60, 69	
Race			8.5
Non-black	213 (63%)	10998 (67%)	
Black	123 (37%)	5316 (33%)	
Year of recurrence			-10.0
Median	2010	2011	
Q1, Q3	2006, 2014	2007, 2014	
PSA at recurrence			-2.9
Median	0.3	0.3	
Q1, Q3	0.2, 0.6	0.2, 0.4	
PCCI at recurrence			-3.7
<=4	206 (61%)	10296 (63%)	
>=5	130 (39%)	6018 (37%)	
D'Amico Risk			10.1
Low/Intermediate risk	171 (51%)	9125 (56%)	
High risk	165 (49%)	7189 (44%)	
XRT			-34.1
No	92 (27%)	7093 (43%)	
Yes	244 (73%)	9221 (57%)	
Follow-up from start of ADT or matched PSA			24.8
Median	58.4	35.0	
Q1, Q3	27.7, 108.7	11.2, 83.0	

Supplementary Table 1e: Patient Characteristics of Early ADT Patients and up to 82 Matched Controls

Patient Characteristics of Early ADT Patients and up to 82 Matched Controls

	Early ADT Patient (N=336)	Matched Control (N=19,408)	Standardized Differences, %
Age at recurrence			-22.8
Median	63	65	
Q1, Q3	59, 67	60, 69	
Race			7.8
Non-black	213 (63%)	13026 (67%)	
Black	123 (37%)	6382 (33%)	
Year of recurrence			-13.5
Median	2010	2011	
Q1, Q3	2006, 2014	2007, 2014	
PSA at recurrence			-2.7
Median	0.3	0.3	
Q1, Q3	0.2, 0.6	0.2, 0.4	
PCCI at recurrence			-6.5
<=4	206 (61%)	12511 (64%)	
>=5	130 (39%)	6897 (36%)	
D'Amico Risk			16.9
Low/Intermediate risk	171 (51%)	11505 (59%)	
High risk	165 (49%)	7903 (41%)	
XRT			-33.1
No	92 (27%)	8340 (43%)	
Yes	244 (73%)	11068 (57%)	
Follow-up from start of ADT or matched PSA			27.2
Median	58.4	34.5	
Q1, Q3	27.7, 108.7	10.7, 80.4	

Supplementary Table 1f: Patient Characteristics of Early ADT Patients and All Potential Matched Controls

Patient Characteristics of Early ADT Patients and All Potential Matched Controls

	Early ADT Patient (N=336)	Matched Control (N=21,221)	Standardized Differences, %
Age at recurrence			-20.8
Median	63	65	
Q1, Q3	59, 67	60, 69	
Race			7.4
Non-black	213 (63%)	14203 (67%)	
Black	123 (37%)	7018 (33%)	
Year of recurrence			-14.0
Median	2010	2011	
Q1, Q3	2006, 2014	2007, 2014	
PSA at recurrence			-5.1
Median	0.3	0.3	
Q1, Q3	0.2, 0.6	0.2, 0.4	
PCCI at recurrence			-11.6
<=4	206 (61%)	14190 (67%)	
>=5	130 (39%)	7031 (33%)	
D'Amico Risk			23.9
Low/Intermediate risk	171 (51%)	13297 (63%)	
High risk	165 (49%)	7924 (37%)	
XRT			-32.9
No	92 (27%)	9097 (43%)	
Yes	244 (73%)	12124 (57%)	
Follow-up from start of ADT or matched PSA			27.5
Median	58.4	35.2	
Q1, Q3	27.7, 108.7	10.7, 80.4	