# Competing Risks of Mortality Among Men with Biochemical Recurrence after Radical Prostatectomy

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# Understanding Competing Risks of Mortality in Men with Recurrence after Radical Prostatectomy

- Biochemical recurrence (BCR) after radical prostatectomy (RP) is common, with annual incidence of 29,000 cases

- Previous work has shown that men with BCR are unlikely to die of their disease, with 5-, 10-, 15-year prostate cancer-specific mortality (PCSM) rates of 3%, 11%, and 21%.

- Rates of PCSM and other-cause mortality (OCM) by key clinical predictors are lacking

- Information on competing risks of mortality may assist in assessment of prognosis and identification of men who may benefit from delayed ADT



Uchio et al, Arch Int Med 2010

# Study Design

- Goal: To define long-term competing risks of mortality in men with BCR after RP by key clinical predictors of PCSM, metastasis, and OCM

- Sample: 1,225 men with BCR after RP between 2000-17 in the SEARCH database

- Statistical Methods:
  - Multivariable competing risks regression analysis
  - Recursive partitioning analysis

- Predictors:
  - Sociodemographics: Age, Charlson comorbidity index score, Race, location
  - Biochemical Markers: PSA-DT (<9 mos vs. ≥9 mos), PSA at BCR
  - Tumor Variables: Pre-operative D'Amico tumor risk, Pathological grade and stage, surgical margin status
  - Clinical Variables: Receipt of salvage XRT

- Outcomes: Prostate cancer mortality, metastasis, and other-cause mortality

# Cohort Attrition

SEARCH database
N=7,811

- Unknown recurrence (N=29)
- No recurrence (N=5,093)
- Recurrence due to treatment (N=498)
- Recurrence due to metastases (N=7)
- Missing date of recurrence (N=2)

Had a biochemical recurrence
N=2,182

- Biochemical recurrence prior to 2001 (N=701)

Had a biochemical recurrence 2001-2018
N=1,481

- Positive lymph nodes (N=91)
- Missing PSA at recurrence (N=3)
- Missing pathological grade group (N=25)
- Missing D'Amico risk group (N=108)
- Missing surgical margins status (N=9)
- Missing pathological stage (N=8)
- Missing race (N=12)

Analysis cohort
N=1,225



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# Study Sample

- Age at BCR:  65 (IQR 60, 69)

- Charlson comorbidity index score:
  - 0:  346 (28%)
  - 1:  267 (22%)
  - 2:  206 (17%)
  - 3+:  406 (33%)

- Pre-Operative D'Amico tumor risk:
  - Low:  278 (23%)
  - Intermediate:  520 (42%)
  - High:  427 (35%)

- Median follow up from BCR:  5.6 years (IQR 2.7, 9.1)
  - Death from other causes: 243/1,225 (20%)
  - Death from prostate cancer: 68/1,225 (6%)

# Competing Risks Regression: Time from BCR to PCSM and Metastasis

## PCSM

| | SHR | 95% CI | p-value |
|---|---|---|---|
| **D'Amico risk group** | | | <0.001 |
| Low | Ref. | | |
| 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 at BCR** | | | <0.001 |
| ≥9 months | Ref. | | |
| <9 months | 2.46 | 1.22-4.96 | |
| Unknown | 3.41 | 1.90-6.12 | |
| **Salvage radiation** | 0.45 | 0.28-0.73 | 0.001 |

## Metastasis

| | SHR | 95% CI | p-value |
|---|---|---|---|
| **D'Amico risk group** | | | 0.001 |
| Low | Ref. | | |
| Intermediate | 2.27 | 1.18-4.36 | |
| High | 3.35 | 1.73-6.48 | |
| **PSA at BCR** | 1.56 | 1.33-1.82 | <0.001 |
| **PSADT at BCR** | | | 0.001 |
| ≥9 months | Ref. | | |
| <9 months | 2.28 | 1.41-3.70 | |
| Unknown | 1.97 | 1.29-3.03 | |
| **Path grade group** | | | 0.013 |
| 1 | Ref. | | |
| 2 | 1.46 | 0.72-2.96 | |
| 3 | 1.87 | 0.89-3.94 | |
| 4-5 | 2.74 | 1.31-5.71 | |

Additional covariates: Age at BCR, Charlson Comorbidity Index at BCR, surgical margin status, pathological stage, race, receipt of salvage radiation therapy, surgery center, year of BCR



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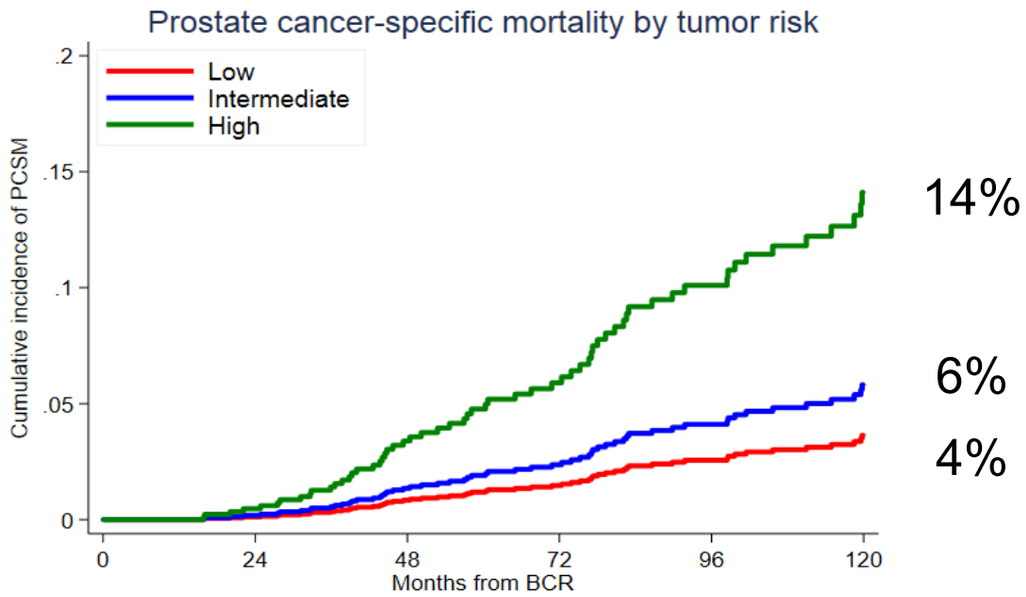
# Cumulative Incidence of PC Mortality and Metastasis after BCR by D'Amico tumor risk and PSA-DT

## PCSM

## Metastasis

Tumor Risk

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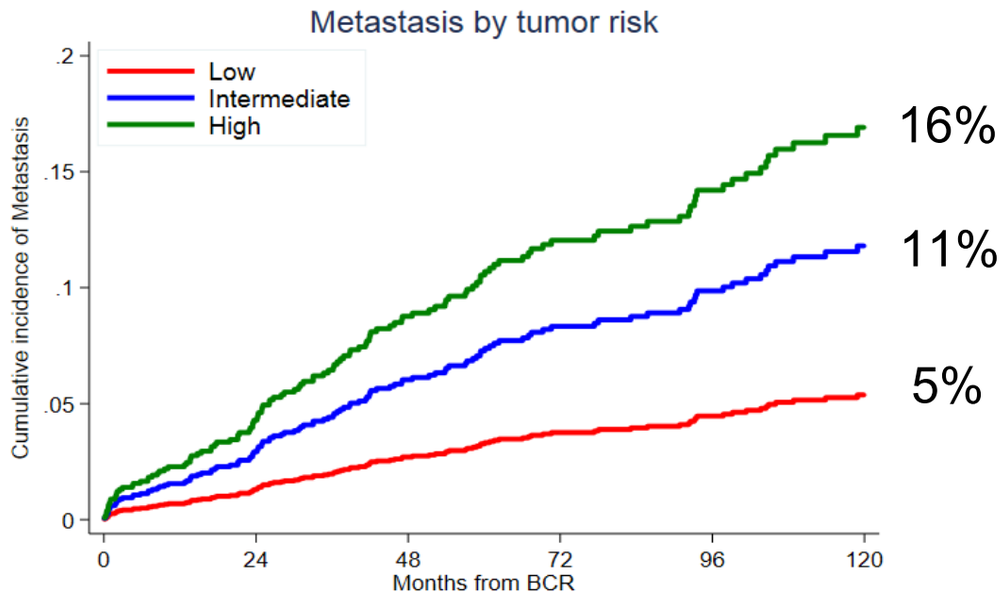


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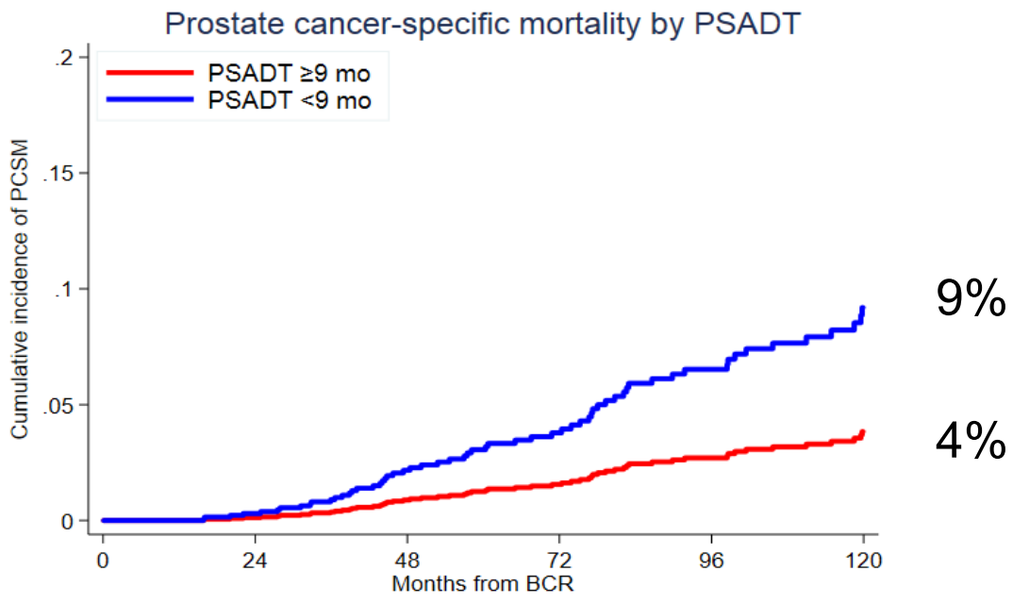
PSA-DT

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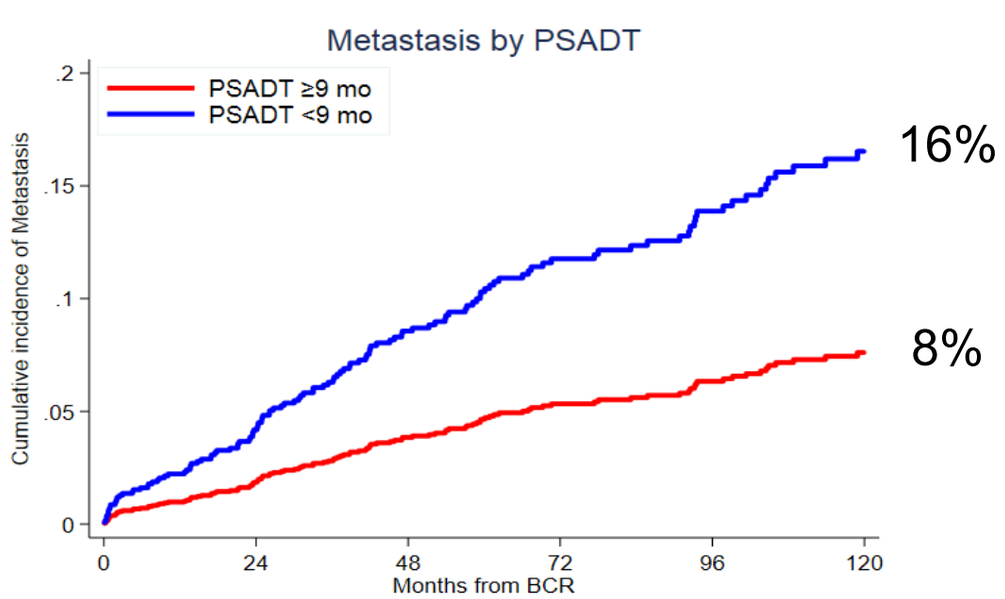


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# Competing Risks Regression: Time from BCR to Other-Cause Mortality

| | SHR | 95% CI | p-value |
|---|---|---|---|
| **Age at BCR** | | | <0.001 |
| **<65** | Ref. | | |
| **65-69** | 1.30 | 0.92-1.82 | |
| **≥70** | 2.08 | 1.52-2.83 | |
| **CCI at BCR** | | | <0.001 |
| **0** | Ref. | | |
| **1** | 1.61 | 1.08-2.40 | |
| **2** | 1.59 | 1.03-2.45 | |
| **3+** | 2.40 | 1.68-3.44 | |
| **Year of BCR** | 0.92 | 0.89-0.96 | <0.001 |
| **Surgery Center** | | | 0.010 |
| **West LA** | Ref. | | |
| **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 Radiation** | 0.42 | 0.32-0.54 | <0.001 |

Additional covariates: D'Amico tumor risk, pathological grade group and stage, log PSA at BCR, PSA-DT at BCR, surgical margin status, race, receipt of salvage radiation therapy, surgery center, year of BCR



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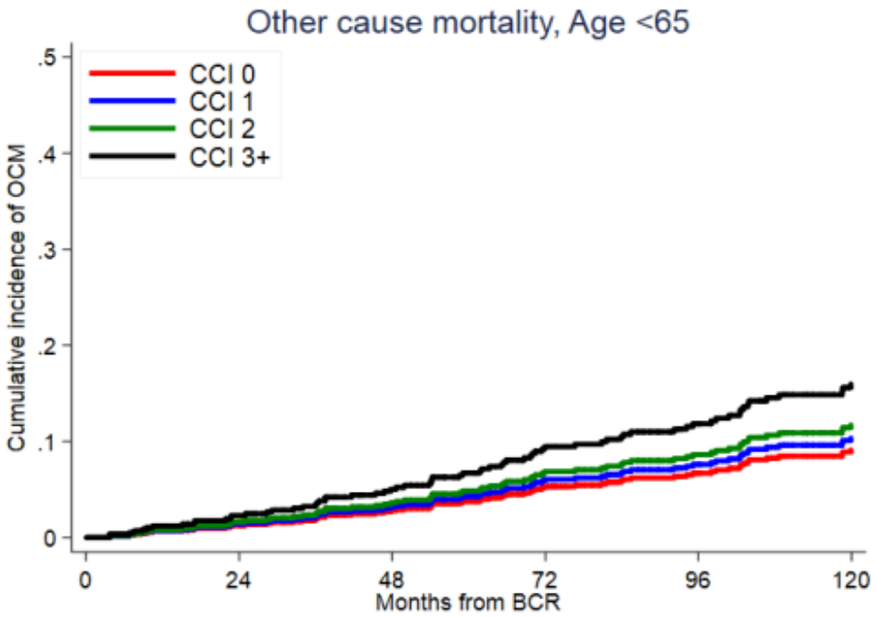
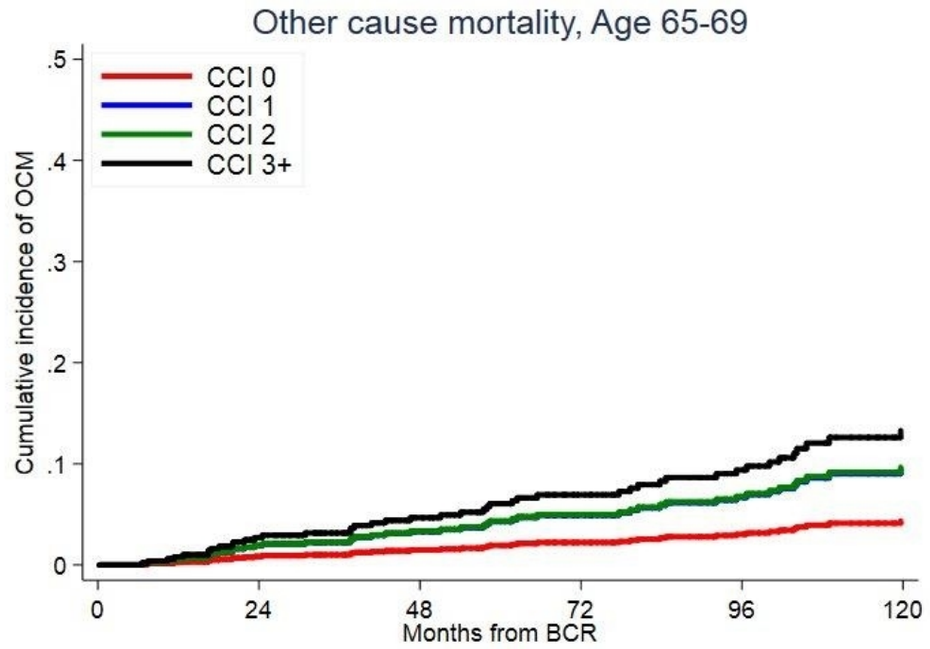
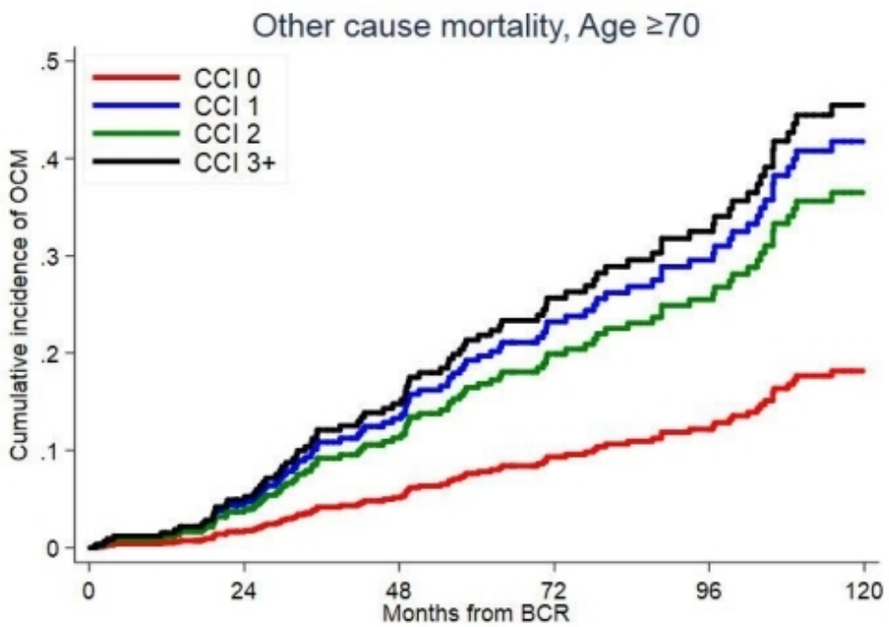
# Cumulative Incidence of Other-Cause Mortality by Age and Charlson Comorbidity Index Score at BCR

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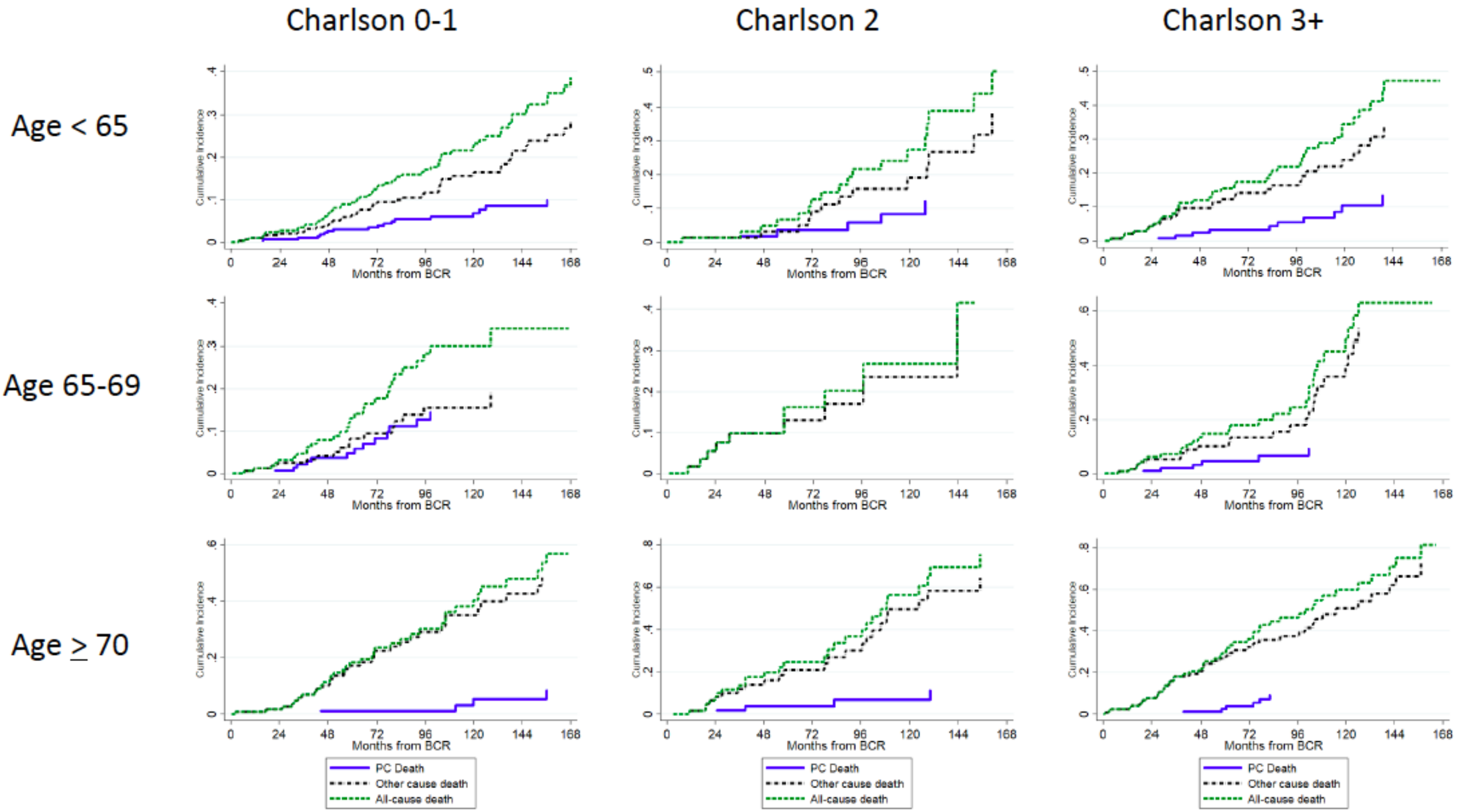
# Competing Risks of Mortality by Age and Charlson Comorbidity Index Score at BCR



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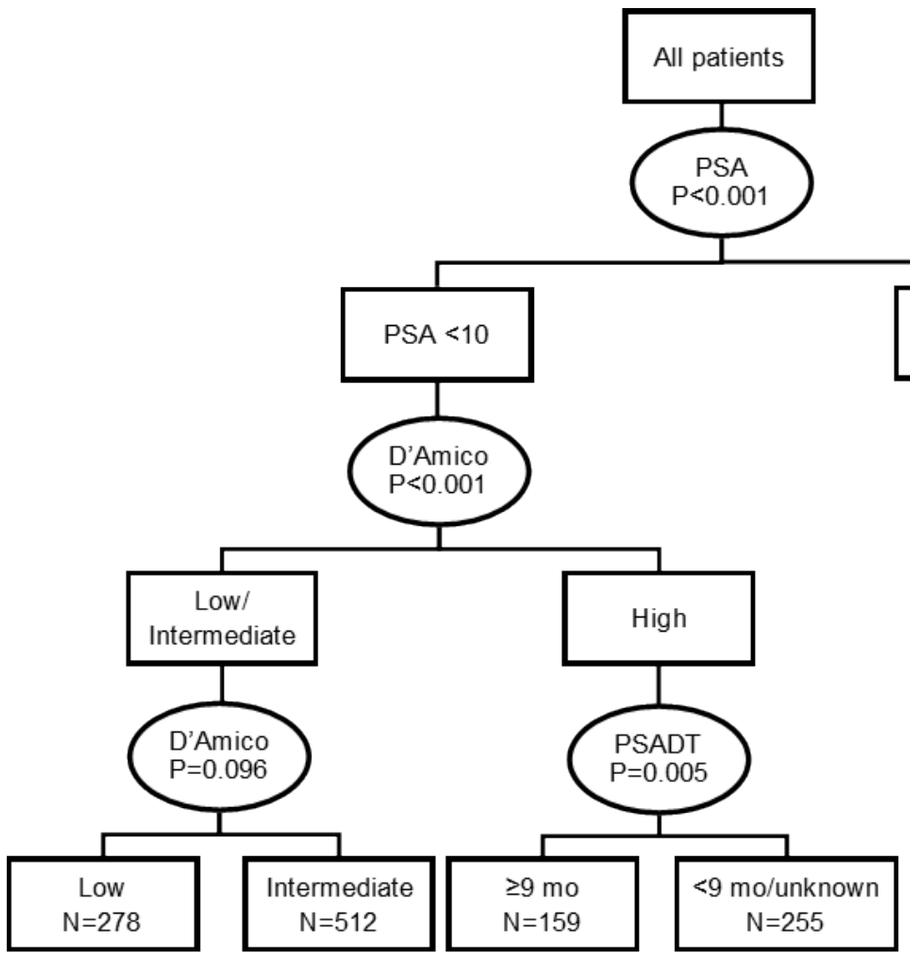
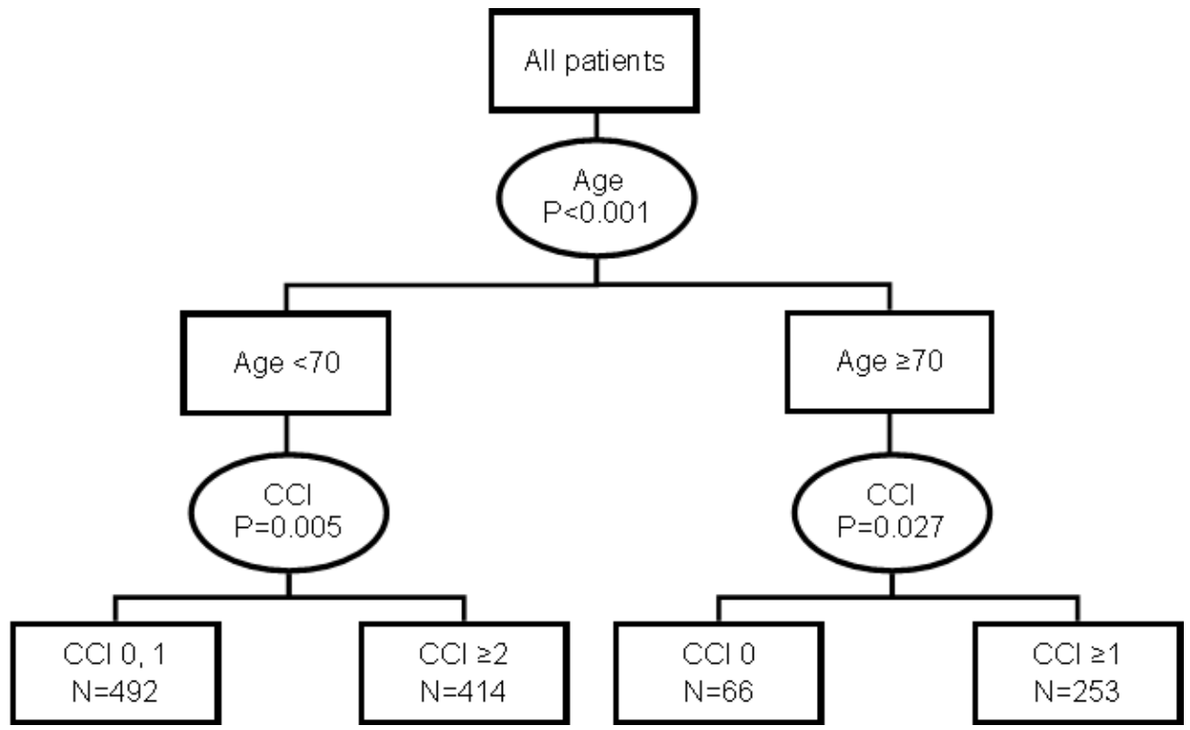
# Recursive Partitioning Analysis to Identify Optimal Cutpoints for Prediction of PCSM and OCM

## PCSM




## Other-Cause Mortality



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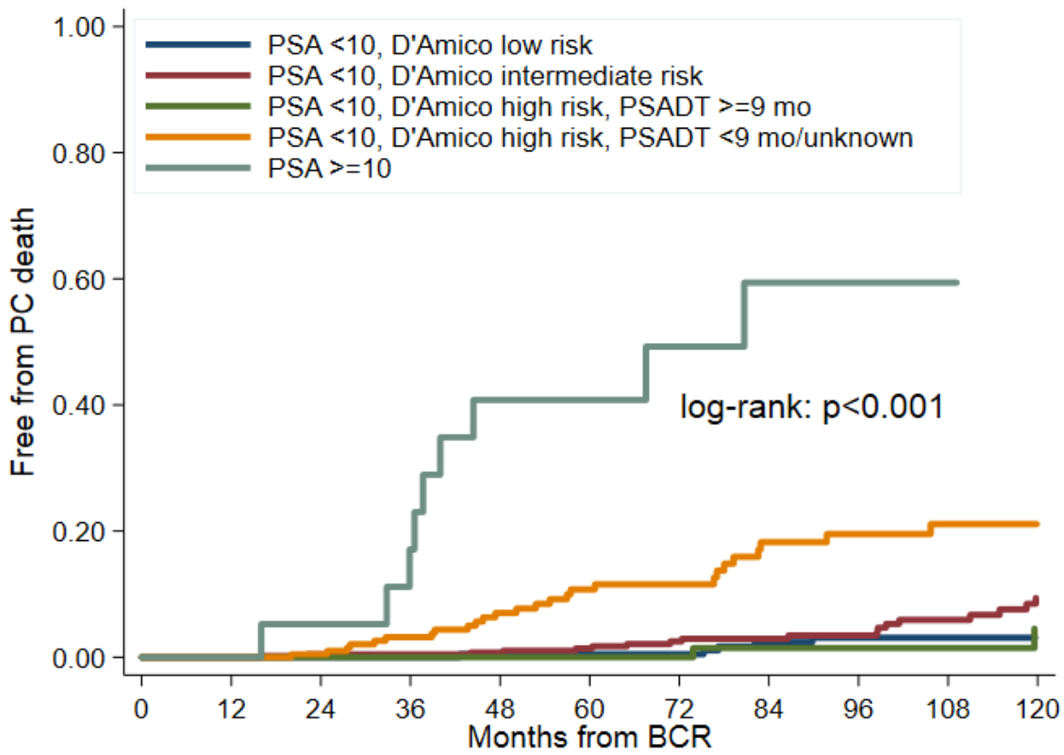
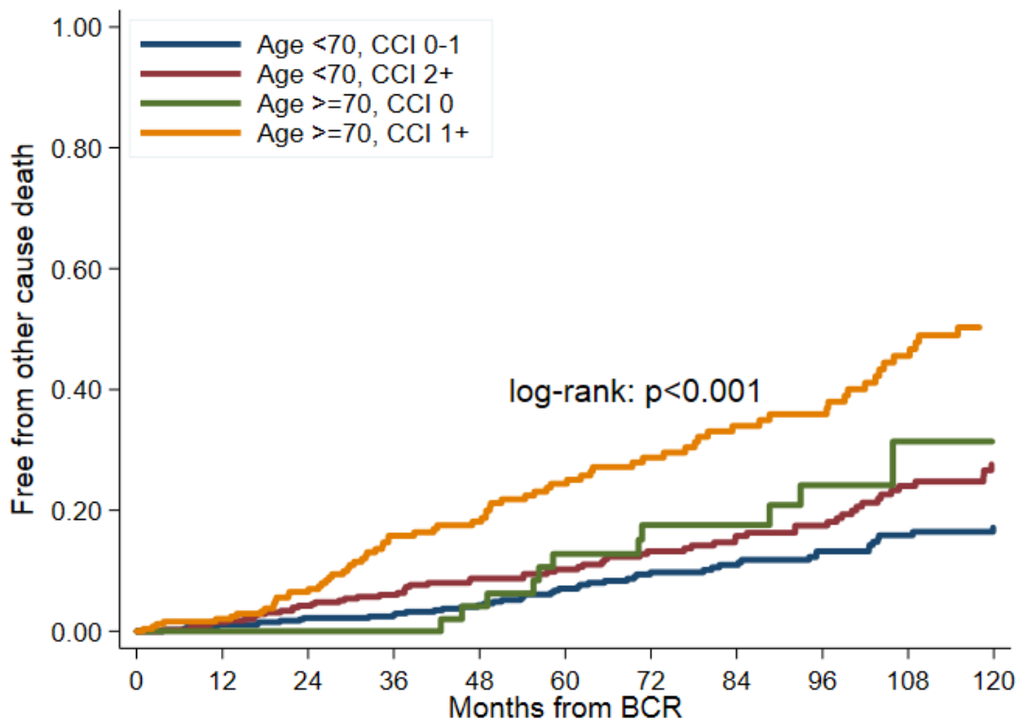
# Cumulative Incidence of PCSM and OCM by Recursive Partitioning Subgroups

## PCSM




## Other-Cause Mortality



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# Summary

- 10-year cumulative incidence of PCSM and metastasis among those with BCR after RP is low, even among those at highest risk

- 10-year cumulative incidence of OCM is low for the majority of patients, except those 70 years or older with any degree of comorbidity (>40%)

- Recursive partitioning analysis empirically validated these groupings:
  - Men at highest risk for PCSM: PSA-DT<9 months, high D'Amico risk
  - Men at highest risk for OCM: >70 years with any major comorbidity

# Applications

- Individualize prognosis for men with BCR after RP
- Inform comparative effectiveness studies of early vs. delayed ADT in men with BCR after RP
  - Men at low risk for PCSM and high risk for OCM may benefit less from early or intensified ADT

# Conclusions

- Significant heterogeneity in prognosis among men with BCR after RP can be explained by clinical variables

- Men in their 70s with any major comorbidity are 2-10x more likely to die of other causes than prostate cancer despite BCR

- Integration of this information into clinical practice may help patients and physicians better understand their disease