



Persistent PSA Following Radical Prostatectomy for Prostate Cancer and Mortality Risk

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Research

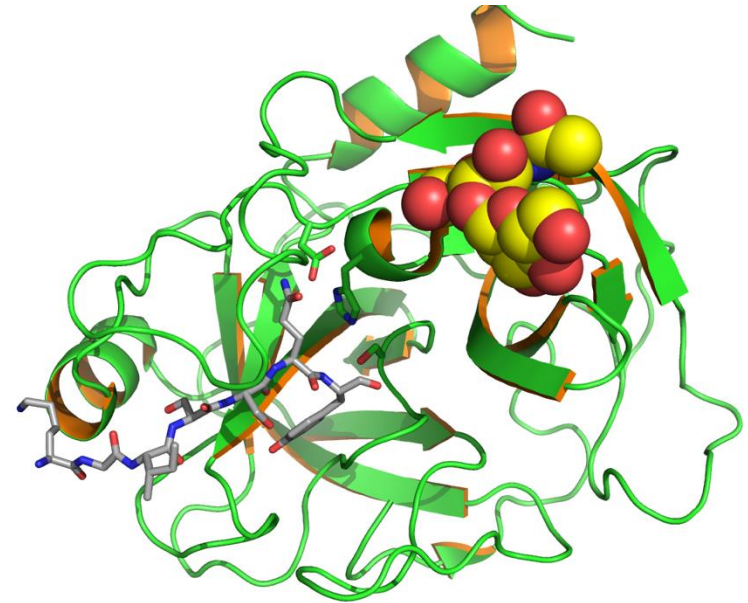
JAMA Oncology | **Original Investigation**

Persistent Prostate-Specific Antigen Following Radical Prostatectomy for Prostate Cancer and Mortality Risk

Derya Tilki, MD; Ming-Hui Chen, PhD; Jing Wu, PhD; Hartwig Huland, MD; Markus Graefen, MD;
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PSA Clearance Following RP

- PSA $\frac{1}{2}$ life: 2–3 days
- Undetectable PSA levels expected 1–2 months post-RP
- Persistent PSA post-RP → Worse survival outcomes

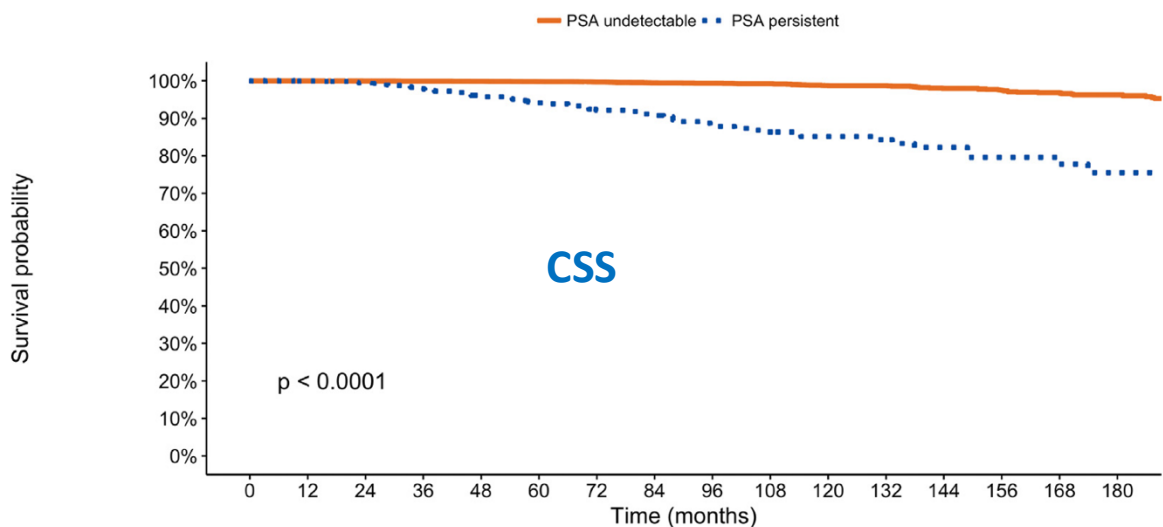


Persistent Prostate-Specific Antigen After Radical Prostatectomy and Its Impact on Oncologic Outcomes

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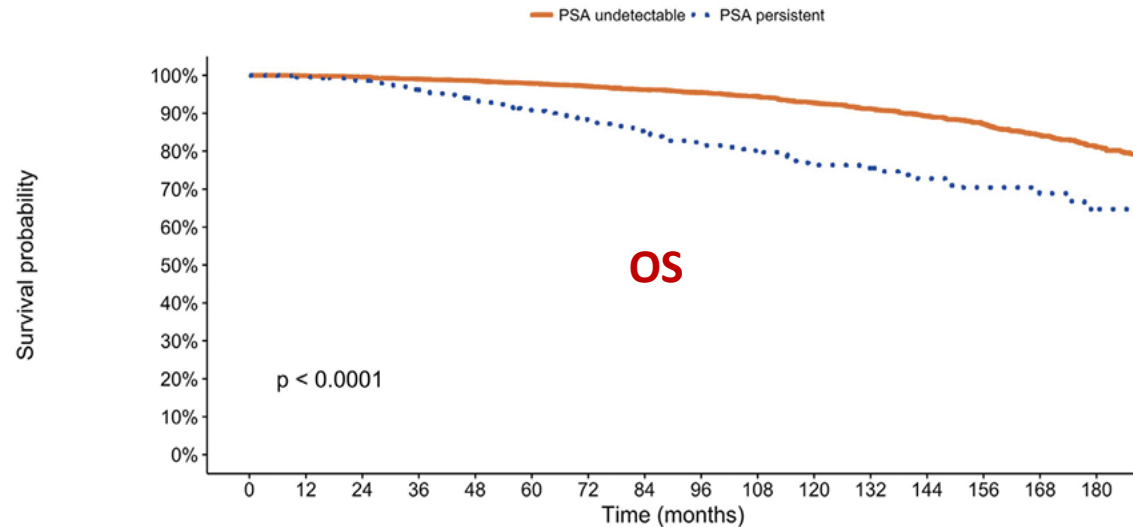
Cancer-specific survival



Number at risk

| Time (months) | 0 | 12 | 24 | 36 | 48 | 60 | 72 | 84 | 96 | 108 | 120 | 132 | 144 | 156 | 168 | 180 |
|------------------|-------|------|------|------|------|------|------|------|------|------|------|------|------|------|-----|-----|
| PSA undetectable | 10494 | 9943 | 8967 | 7916 | 6913 | 5902 | 5012 | 4144 | 3337 | 2663 | 2102 | 1675 | 1316 | 1023 | 746 | 530 |
| PSA persistent | 1020 | 913 | 745 | 602 | 498 | 388 | 321 | 256 | 207 | 167 | 131 | 94 | 74 | 58 | 43 | 30 |

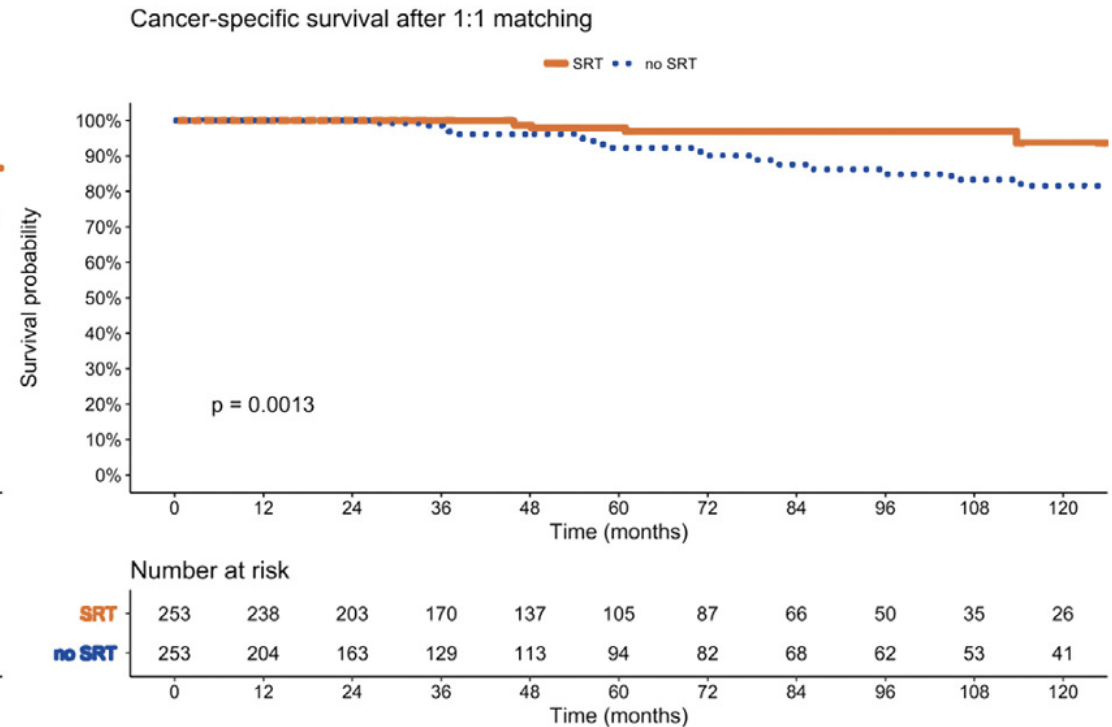
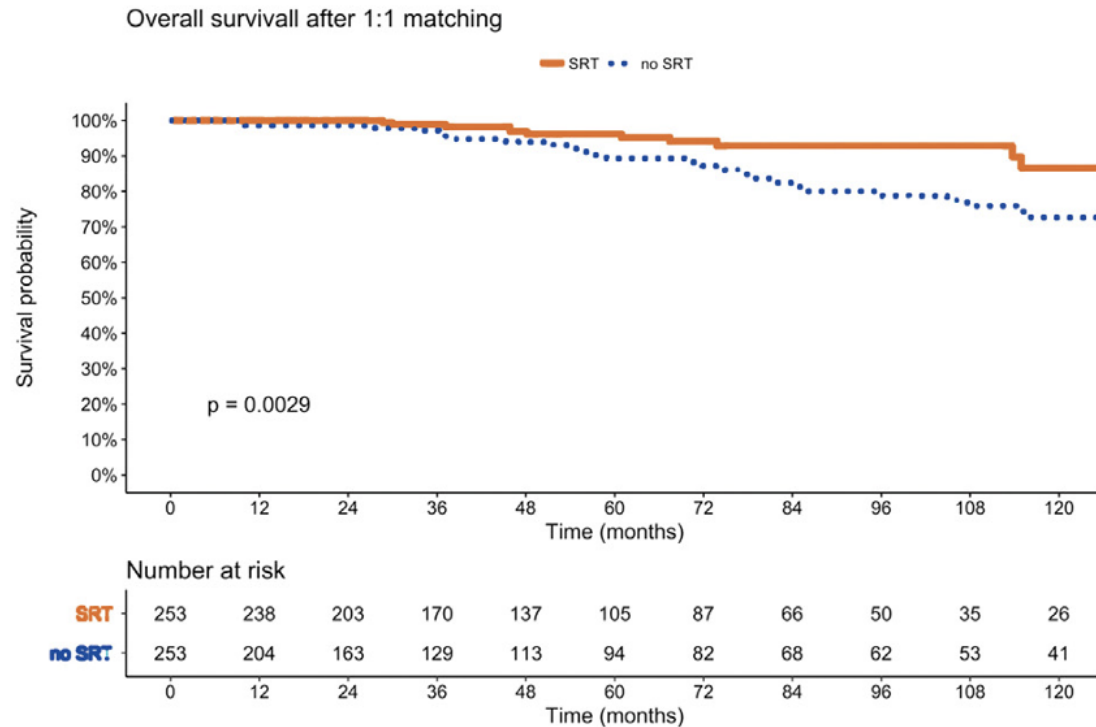
Overall survival



Number at risk

| Time (months) | 0 | 12 | 24 | 36 | 48 | 60 | 72 | 84 | 96 | 108 | 120 | 132 | 144 | 156 | 168 | 180 |
|------------------|-------|-------|------|------|------|------|------|------|------|------|------|------|------|------|-----|-----|
| PSA undetectable | 10576 | 10024 | 9046 | 7986 | 6977 | 5958 | 5061 | 4186 | 3373 | 2695 | 2131 | 1696 | 1334 | 1040 | 758 | 538 |
| PSA persistent | 1025 | 918 | 750 | 604 | 499 | 389 | 322 | 256 | 207 | 167 | 131 | 94 | 74 | 58 | 43 | 30 |

Persistent PSA → Important Implications for Salvage Therapy



sRT in pts w/ persistent PSA → Improved CSS & OS

But...What Timepoint Should be Used to Define PSA Persistence?

- EAU: PSA level is expected to be undetectable two months after a RP
- AUA: 6–8 weeks post-op
- But...should PSA be checked at the same timepoint in all patients?
- Do patients with higher PSA levels pre-RP need more time to clear their serum PSA?
 - **'False positive' findings** → Over-treatment with salvage XRT/ADT → Negative impact on patient QoL

Study Hypotheses

1. Among patients with persistent PSA at 2 months post-RP, pts with pre-RP PSA >20 ng/ml have superior PCSM & ACM, compared to pts with pre-RP PSA ≤ 20 ng/ml
 - Assumption: Some pre-RP PSA >20 ng/mL pts with persistent PSA following RP have 'false positive' persistent PSAs that would clear with extended f/u
2. Increasing persistent PSA level associated with worse PCSM & ACM

Study Cohort & Follow-Up

- **Discovery cohort:** Men who underwent an RP for cT1-3N0M0 PCa at the University Hospital Hamburg-Eppendorf, January 1992 & June 2020
 - Staging using conventional imaging for pts w/ PSA >20 ng/mL and/or GS 8-10
- **Validation cohort:** Similar cohort of RP pts from Johns Hopkins, 1990–2017
- **T0:** Date of RP
- **Follow-up:** PSA q2-3 month 1st year, q6 month next 4 years, annually thereafter

Study Endpoints & Statistical Methods

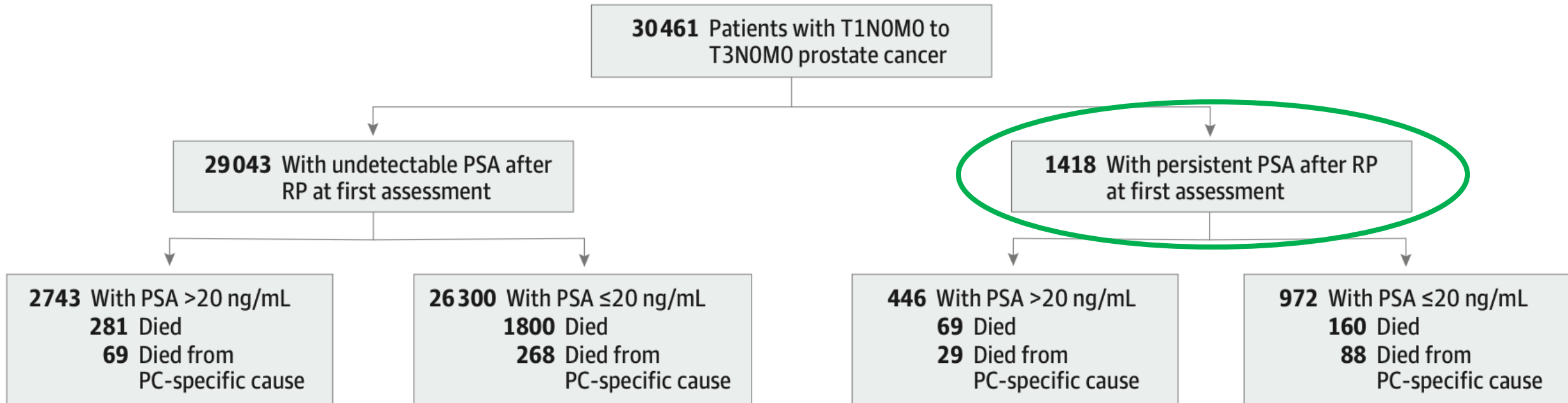
- Co-primary:
 - Prostate cancer-specific mortality (PCSM)
 - All-cause mortality (ACM)
- Survival analyses using Fine and Gray and Cox PH modeling
- Two interaction terms included in regression models:
 1. **Persistent PSA vs undetectable PSA post-RP & pre-RP PSA level >20 vs ≤20 ng/ml** → Evaluate among pts w/ persistent PSA post-RP if pre-RP PSA >20 ng/mL assoc w/ lower PCSM & ACM
 2. **Persistent PSA vs undetectable PSA post-RP & time-dependent post-RP RT or ADT use** → Evaluate whether time-dependent RT or ADT use post-RP assoc w/ PCSM & ACM in both pts w/ undetectable or persistent PSA

Study Endpoints & Statistical Methods (Cont'd)

- Assoc between persistent PSA level & PCSM/ACM evaluated using Fine Gray & CPH models
- MV models adjusted for:
 - Age at RP
 - Year of RP
 - RP GS
 - pT stage
 - Margin status
 - pN status
 - Time-dependent post-RP RT or ADT use
 - Prostate volume (subset)

Significant efforts made
to control for potential
confounders

CONSORT Diagram



Comparison of Clinical Factors Among 30,461 Patients

| Clinical factor | Post-RP PSA, No. (%) | | | P value | |
|--|------------------------------|---|---|--|--|
| | Undetectable (n = 29 043) | Persistent and below median (n = 706) ^a | Persistent and at or above median (n = 712) ^a | Undetectable vs persistent PSA below median ^a | Persistent PSA below median vs at or above median ^a |
| Age at RP, median (IQR), y | 64 (59-68) | 65 (60-69) | 64 (59-69) | .001 | .38 |
| Year of RP, median (IQR) | 2013 (2008-2016) | 2014 (2011-2016) | 2014 (2011-2016) | <.001 | .55 |
| Pre-RP PSA level, median (IQR), ng/mL | 7.97 (5.71-12.00) | 11.73 (7.28-19.69) | 16.50 (10.00-28.93) | <.001 | <.001 |
| Prostate volume, median (IQR), mL ^b | 39.00 (30.00-52.00) | 39.00 (30.00-50.00) | 40.85 (32.00-52.00) | .99 | .02 |
| Pre-RP PSA level, ng/mL | | | | | |
| <4 | 2119 (7.3) | 37 (5.2) | 18 (2.5) | <.001 | <.001 |
| 4-10 | 16 945 (58.4%) | 257 (36.4) | 161 (22.6) | | |
| >10-20 | 7236 (24.9) | 246 (34.8) | 253 (35.5) | | |
| >20 | 2743 (9.4) | 166 (23.5) | 280 (39.3) | | |
| Prostatectomy Gleason score | | | | | |
| 6 | 4621 (15.9) | 44 (6.2) | 18 (2.5) | <.001 | <.001 |
| 7 | 22 591 (77.8) | 505 (71.5) | 440 (61.8) | | |
| 8-10 | 1831 (6.3) | 157 (22.2) | 254 (35.7) | | |
| Prostatectomy T category | | | | | |
| T2 | 19 060 (65.6) | 215 (30.45) | 89 (12.5) | <.001 | <.001 |
| T3a | 6379 (22.0) | 189 (26.8) | 175 (24.6) | | |
| pT3b/4 | 3604 (12.4) | 302 (42.8) | 448 (62.9) | | |
| Margin status | | | | | |
| Negative | 23 701 (81.6) | 391 (55.4) | 306 (43.0) | <.001 | <.001 |
| Positive | 5342 (18.4) | 315 (44.6) | 406 (57.0) | | |
| Prostatectomy pelvic lymph node disease | | | | | |
| Negative | 26 641 (91.7) | 484 (68.6) | 333 (46.8) | <.001 | <.001 |
| Positive | 2402 (8.3) | 222 (31.4) | 379 (53.2) | | |
| Adjuvant or salvage therapy ^c | | | | | |
| RT | 5915 (20.4) | 440 (62.3) | 440 (61.8) | NA | NA |
| ADT | 3469 (11.9) | 321 (45.5) | 532 (74.7) | NA | NA |
| All-cause deaths ^c | 2081 (7.2) | 84 (11.9) | 145 (20.4) | NA | NA |
| All-cause deaths from prostate cancer ^c | 337 (16.2) | 31(36.9) | 86 (59.3) | NA | NA |

0.37 ng/mL

Characterization of Persistent PSA and Time to Undetectable PSA by Pre-RP PSA Levels (n=1,418)

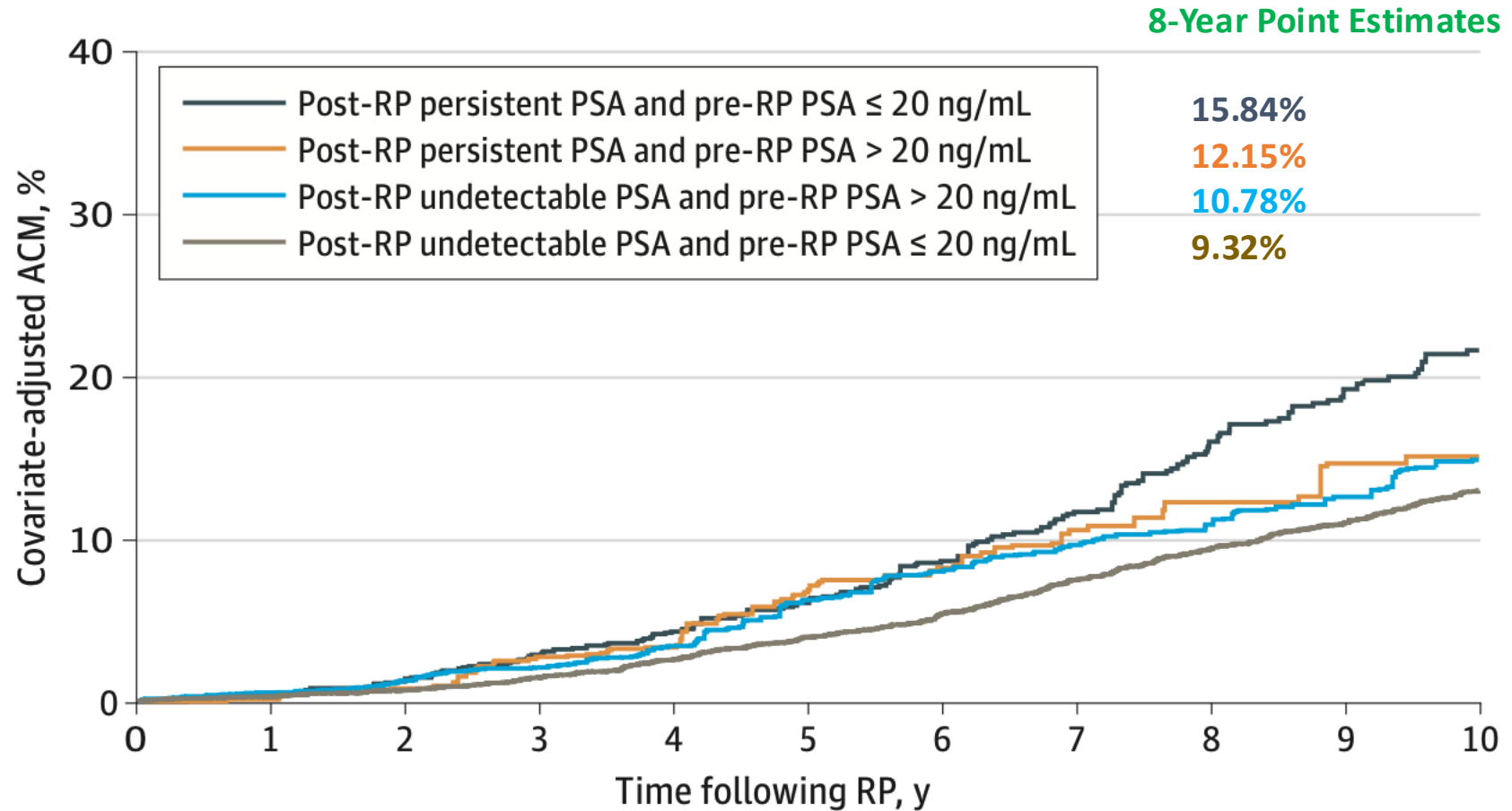
| Characteristic | Pre-RP PSA ≤20 ng/mL | Pre-RP PSA >20 ng/mL | All patients with a persistent PSA |
|---|----------------------|----------------------|------------------------------------|
| Pre-RP PSA level, median (IQR), ng/mL | 10.26 (6.98-13.95) | 35.00 (25.60-56.00) | 13.51 (8.60-24.77) |
| Patients with persistent PSA, No./total No. (%) ^a | 972/27 272 (3.6) | 446/3189 (14.0) | 1418/30 461 (4.7) |
| Persistent PSA level, median (IQR), ng/mL ^a | 0.30 (0.12-1.00) | 0.65 (0.22-2.04) | 0.37 (0.15-1.37) |
| * Time from RP to first assessment for a persistent PSA level, median (IQR), mo ^b | 2.23 (1.45-3.06) | 2.00 (1.41-2.99) | 2.17 (1.45-3.02) |
| * Time between the first and second PSA assessments, median (IQR), mo ^b | 2.30 (0.92-4.01) | 2.25 (0.79-3.99) | 2.30 (0.85-4.01) |
| * Time from RP to an undetectable PSA in patients with a persistent PSA observed for 6 mo following RP ^b | | | |
| Median (IQR), mo | 3.37 (2.35-4.09) | 2.96 (1.84-3.29) | 3.22 (2.27-4.04) |
| No./total No. (%) | 68/972 (7.0) | 15/446 (3.4) | 83/1418 (5.9) |
| * Time to initiation of RT within 1 y of RP for a persistent PSA ^{b,c} | | | |
| Median (IQR), mo | 4.47 (3.42-5.95) | 3.84 (3.19-5.03) | 4.19 (3.29-5.63) |
| No./total No. (%) | 481/972 (49.5) | 279/446 (62.6) | 760/1418 (52.9) |
| * Time to initiation of ADT within 1 y of RP for a persistent PSA ^{b,d} | | | |
| Median (IQR), mo | 3.30 (2.00-5.39) | 2.68 (1.51-4.40) | 3.02 (1.77-5.03) |
| No./total No. (%) | 338/972 (34.8) | 244/446 (54.7) | 582/1418 (41.0) |
| Patients receiving ADT plus RT, No./total No. (%) ^b | 224/972 (23.1) | 165/446 (37.0) | 389/1418 (27.4) |
| Patients with persistent PSA who received RT and/or ADT >1 y following RP, No./total No. (%) ^b | 258/972 (26.5) | 89/446 (20.0) | 347/1418 (24.5) |
| Patients with a persistent PSA level and no post-RP therapy, No./total No. (%) ^b | 192/972 (19.8) | 39/446 (8.7) | 231/1418 (16.3) |

Multivariable Interaction Regression Model Adjusted Hazard Ratios for ACM and PCSM

Median Follow-Up: 6.23 yrs (IQR 3.59-10.25)

| Clinical factor | Patients, No. | ACM | | | PCSM | | |
|--|------------------|-------------|-------------------------------|---------|-------------------|-------------------------------|---------|
| | | Deaths, No. | aHR (95% CI) ^a | P value | PC deaths, No. | aHR (95% CI) ^a | P value |
| Persistent PSA as a categorical covariate | | | | | | | |
| Interaction term: persistent vs undetectable post-RP PSA × pre-RP PSA >20 ng/mL vs ≤20 ng/mL | 30 461 | 2310 | 0.58 (0.43-0.80) | <.001 | 454 | 0.52 (0.30-0.90) | .02 |
| Pre-RP PSA >20 ng/mL | | | | | | | |
| Persistent PSA | 446 | 69 | 0.98 (0.66-1.44) | .90 | 29 | 3.47 (1.54-7.85) | NA |
| Undetectable PSA | 2743 | 281 | 1.0 [Reference] | NA | 69 | 1.0 [Reference] | .003 |
| Pre-RP PSA ≤20 ng/mL | | | | | | | |
| Persistent PSA | 972 | 160 | 1.68 (1.25-2.25) | <.001 | 88 | 6.67 (3.67-12.15) | <.001 |
| Undetectable PSA | 26 300 | 1800 | 1.0 [Reference] | NA | 268 | 1.0 [Reference] | NA |
| Post-RP persistent PSA | | | | | | | |
| Pre-RP PSA >20 ng/mL | 446 | 69 | 0.69 (0.51-0.91) ^b | .01 | 29 | 0.41 (0.25-0.66) ^b | <.001 |
| Pre-RP PSA ≤20 ng/mL | 972 | 160 | 1.0 [Reference] | NA | 88 | 1.0 [Reference] | NA |
| Post-RP undetectable PSA | | | | | | | |
| Pre-RP PSA >20 ng/mL | 2743 | 281 | 1.18 (1.03-1.34) | .017 | 69 | 0.79 (0.60-1.05) | .10 |
| Pre-RP PSA ≤20 ng/mL | 26 300 | 1800 | 1.0 [Reference] | NA | 268 | 1.0 [Reference] | NA |
| Adjuvant or salvage therapy use | | | | | | | |
| Interaction term: persistent vs undetectable post-RP PSA × RT (time-dependent) | 6795 | 613 | 0.87 (0.64-1.17) | .34 | 248 | 0.54 (0.33-0.87) | .01 |
| RT(time-dependent) | | | | | | | |
| Undetectable post-RP PSA | 5915 | 483 | 0.76 (0.67-0.87) | <.001 | 186 | 1.03 (0.78-1.37) | .82 |
| Persistent post-RP PSA | 880 | 130 | 0.66 (0.50-0.87) | .003 | * 62 | 0.55 (0.36-0.86) | .008 |
| Interaction term: persistent vs undetectable post-RP PSA, ng/ml x ADT (time-dependent) | 4322 | 676 | 1.09 (0.78-1.53) | .62 | 360 | 0.41 (0.21-0.82) | .01 |
| ADT (time-dependent) | | | | | | | |
| Undetectable post-RP PSA | 3469 | 502 | 1.99 (1.74-2.27) | <.001 | 253 | 12.01 (8.33-17.32) | <.001 |
| Persistent post-RP PSA | 853 | 174 | 2.17 (1.57-2.99) | <.001 | 104 | 4.96 (2.69-9.15) | <.001 |
| Persistent PSA as a continuous covariate | | | | | | | |
| * Log-transformed persistent post-RP PSA | 1418 | 229 | 1.14 (1.04-1.24) | .004 | 117 | 1.27 (1.12-1.45) | <.001 |
| Adjuvant or salvage therapy | | | | | | | |
| RT (time-dependent) | 880 | 130 | 0.55 (0.41-0.76) | <.001 | 62 | 0.52 (0.33-0.83) | .006 |
| ADT (time-dependent) | 853 | 174 | 1.74 (1.22-2.49) | .002 | 104 | 4.33 (2.25-8.33) | <.001 |

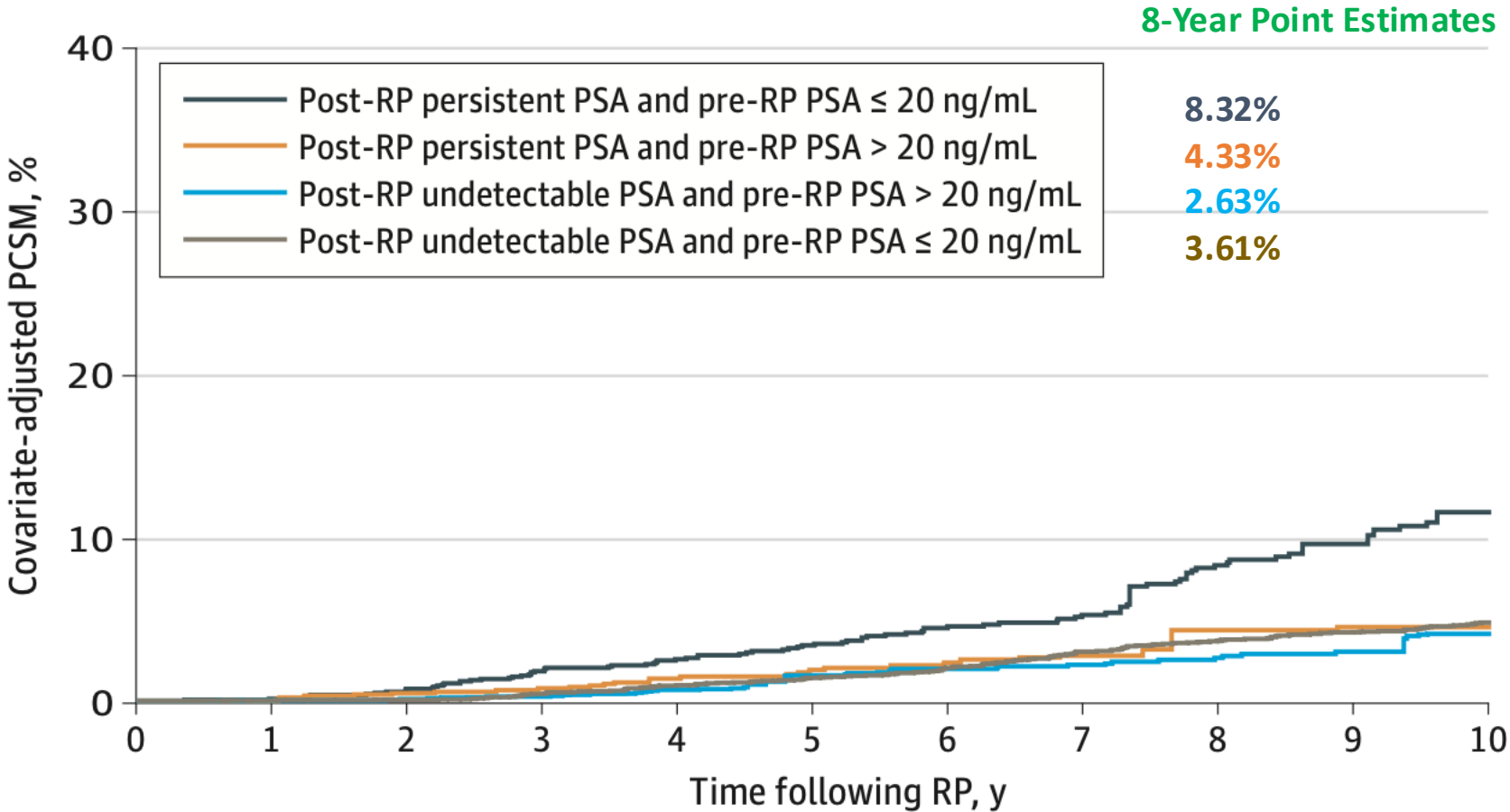
ACM (n=30,461)



No. at risk

| | | | | | | | | | | | |
|----------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|------|------|
| pPSA ≤20 ng/mL | 972 | 898 | 829 | 760 | 676 | 559 | 447 | 354 | 261 | 204 | 156 |
| pPSA >20 ng/mL | 446 | 407 | 377 | 337 | 286 | 238 | 208 | 152 | 114 | 82 | 57 |
| uPSA >20 ng/mL | 2743 | 2486 | 2277 | 2031 | 1664 | 1372 | 1130 | 945 | 761 | 634 | 507 |
| uPSA ≤20 ng/mL | 26300 | 24767 | 23336 | 21643 | 18999 | 16580 | 14440 | 12337 | 10360 | 8775 | 7159 |

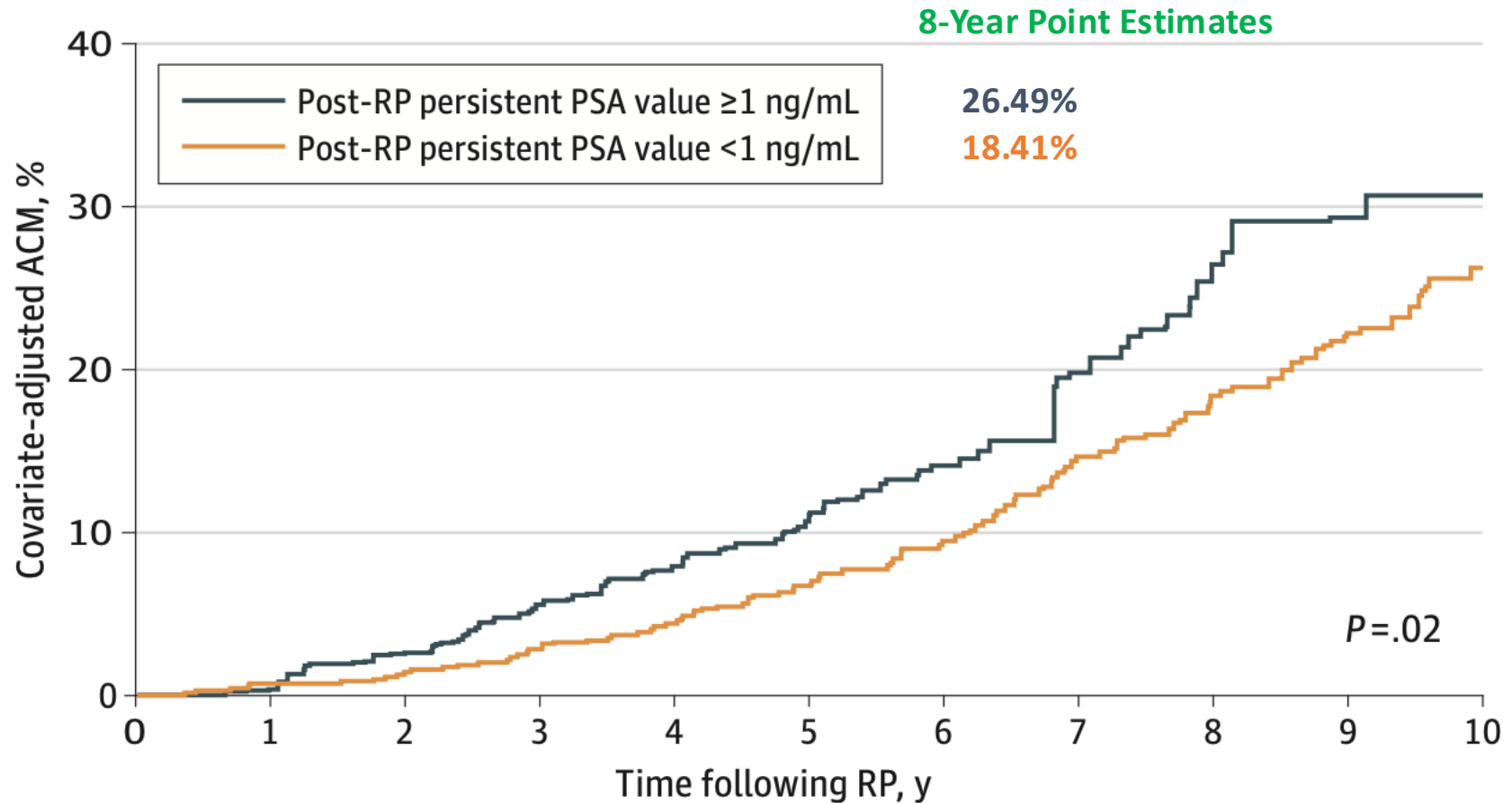
PCSM (n=30,461)



No. at risk

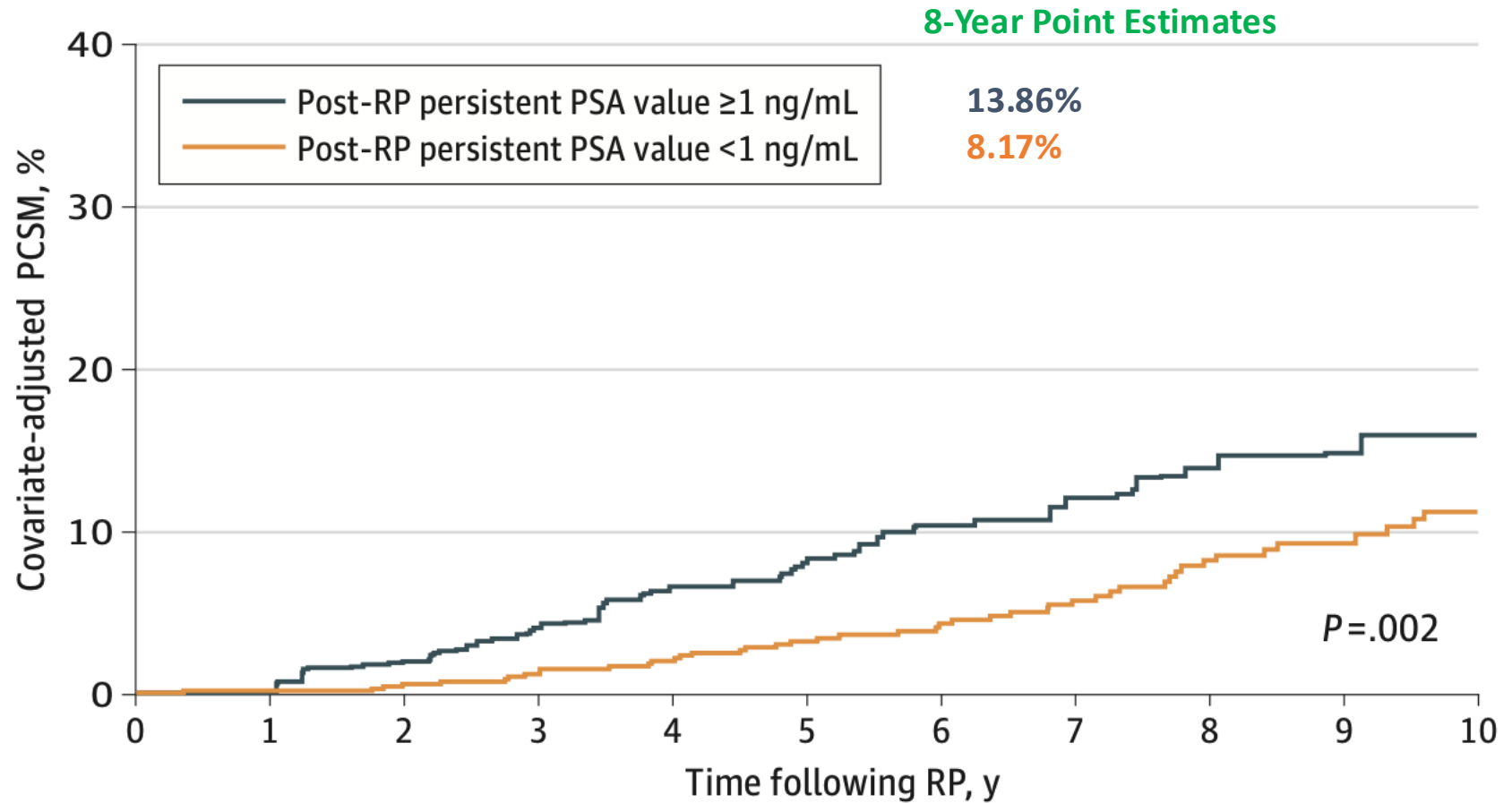
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|----------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|------|------|
| pPSA ≤20 ng/mL | 972 | 898 | 829 | 760 | 676 | 559 | 447 | 354 | 261 | 204 | 156 |
| pPSA >20 ng/mL | 446 | 407 | 377 | 337 | 286 | 238 | 208 | 152 | 114 | 82 | 57 |
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| uPSA ≤20 ng/mL | 26300 | 24767 | 23336 | 21643 | 18999 | 16580 | 14440 | 12337 | 10360 | 8775 | 7159 |

ACM Among Patients with a Post RP Persistent PSA (n=1,418)



| No. at risk | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|-------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| ≥1 ng/mL | 429 | 380 | 349 | 306 | 270 | 217 | 180 | 132 | 102 | 81 | 62 |
| <1 ng/mL | 989 | 925 | 857 | 791 | 692 | 580 | 475 | 374 | 273 | 205 | 151 |

PCSM Among Patients with a Post RP Persistent PSA (n=1,418)



No. at risk

| | | | | | | | | | | | |
|----------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| ≥ 1 ng/mL | 429 | 380 | 349 | 306 | 270 | 217 | 180 | 132 | 102 | 81 | 62 |
| < 1 ng/mL | 989 | 925 | 857 | 791 | 692 | 580 | 475 | 374 | 273 | 205 | 151 |

Discussion

- A counterintuitive association was observed between a significantly lower ACM risk and PCSM risk in patients with a persistent PSA assessed at a median of 2.17 mos post-RP and pre-RP PSA >20 ng/mL vs < 20 ng/mL
 - Hypothesis: more patients with a pre-RP PSA >20 ng/mL assessed for a persistent PSA at a conventional 1.5-2.0 month time point post-RP could have reached an undetectable PSA level if further PSA assessment was done before initiating post-RP therapy for presumed persistent PSA
- Evidence:
 - Patients with pre-RP PSA > 20 ng/mL had earlier PSA assessments following RP → prompt physicians to initiate post-RP therapy sooner
 - Substantiated by more frequent and shorter median time to post-RP RT + ADT use during the 1st year following RP
- **Clinical significance**: need to monitor PSA after RP for longer than 1.5-2.0 mos before concluding a persistent PSA exists and initiating post-RP therapy → *minimize overtreatment*
 - No MFS benefit for adjuvant vs early salvage RT (RCTs, ARTISTIC meta-analysis)

Take Home Message



PSA level assessed for at least 3 months after RP may minimize overtreatment, and in this study, a higher persistent PSA level was associated with a worse prognosis