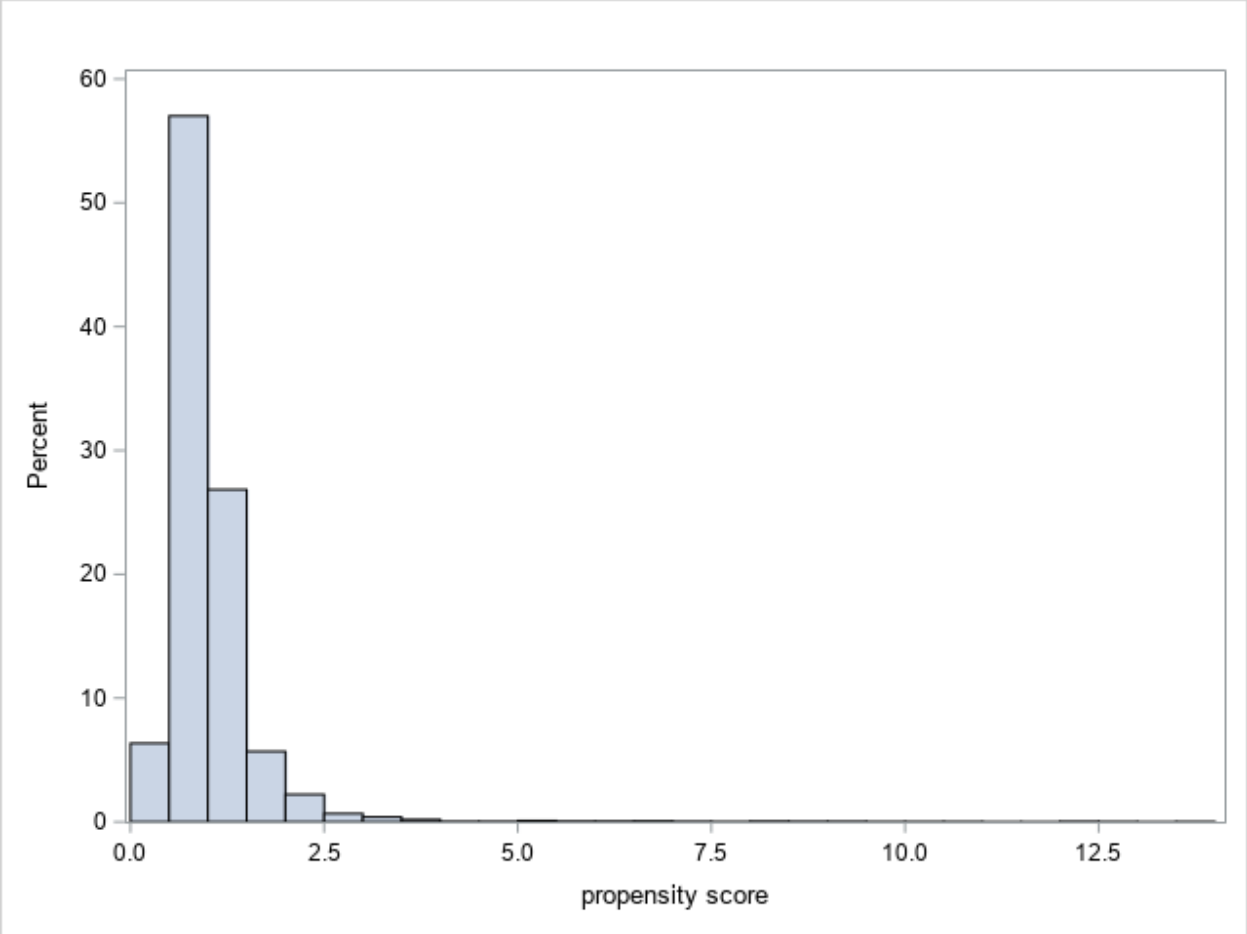
# Supplemental Online Content

Kishan AU, Karnes RJ, Romero T, et al. Comparison of multimodal therapies and outcomes among patients with high-risk prostate cancer with adverse clinicopathologic features. *JAMA Netw Open*. 2021;4(7):e2115312. doi:10.1001/jamanetworkopen.2021.15312



This supplemental material has been provided by the authors to give readers additional information about their work.

**eFigure.** Distribution of Propensity Scores




The mean propensiy score was 0.88 (standard deviation, 0.7), with a median score of 0.88. The range of scores were 0.23-13.68, with an interquartile range of 0.7-1.15.

**eTable 1.** Patient Contribution and Median Follow-up by Overall Treatment Cohort, Stratified by Institution

| Institution | Total 6004 | RP (n=3175) | EBRT (n=1830) | EBRT+BT (n=999) | Median follow-up time (years) (interquartile range) |
|---|---|---|---|---|---|
| University of California, Los Angles | 293 (5 %) | 153 (5 %) | 117 (6 %) | 23 (2 %) | 7.3 (5.6 - 11.8) |
| California Endocurie Therapy Center | 194 (3 %) | 0 (0 %) | 0 (0 %) | 194 (19 %) | 9.2 (5.8 - 13) |
| Fox Chase Cancer Center | 651 (11 %) | 152 (5 %) | 495 (27 %) | 4 (0 %) | 5.5 (3.3 - 8.2) |
| Icahn School of Medicine at Mount Sinai | 146 (2 %) | 0 (0 %) | 14 (1 %) | 132 (13 %) | 7.9 (4.4 - 10.5) |
| Cleveland Clinic | 513 (9 %) | 257 (8 %) | 253 (14 %) | 3 (0 %) | 6.1 (2.8 - 10.2) |
| Wheeling Jesuit University | 58 (1 %) | 0 (0 %) | 0 (0 %) | 58 (6 %) | 8.4 (5.4 - 13.5) |
| University of Michigan | 387 (6 %) | 0 (0 %) | 352 (19 %) | 35 (4 %) | 8.5 (6 - 12.1) |
| Johns Hopkins University School of Medicine | 260 (4 %) | 184 (6 %) | 76 (4 %) | 0 (0 %) | 10.6 (9 - 12.1) |
| Oslo University Hospital | 234 (4 %) | 0 (0 %) | 69 (4 %) | 165 (17 %) | 8 (7 - 9.7) |
| William Beaumont Hospital | 84 (1 %) | 0 (0 %) | 0 (0 %) | 84 (8 %) | 6.2 (4 - 8.3) |
| Chicago Prostate Institute | 81 (1 %) | 0 (0 %) | 0 (0 %) | 81 (8 %) | 8.3 (6 - 13.7) |
| CUN Navarra | 155 (3 %) | 0 (0 %) | 0 (0 %) | 155 (16 %) | 13.8 (11.2 - 15.5) |
| Mayo Clinic | 659 (11 %) | 594 (19 %) | 50 (3 %) | 15 (2 %) | 6 (3.9 - 11.6) |
| Hamburg | 1740 (29 %) | 1740 (55 %) | 0 (0 %) | 0 (0 %) | 3.1 (2 - 5) |
| Princess Margaret Hospital | 346 (6 %) | 0 (0 %) | 342 (19 %) | 4 (0 %) | 10.9 (7.8 - 12.9) |
| University of Utah | 203 (3 %) | 95 (3 %) | 62 (3 %) | 46 (5 %) | 8.9 (5.6 - 12.3) |

EBRT, external beam radiotherapy; EBRT+BT, external beam radiotherapy with brachytherapy boost; n, number; RP, radical prostatectomy

**eTable 2.** Pathological Characteristics and Treatment Details

| | All RP n=3175 | All EBRT n=1830 | All EBRT+BT n=999 | Optimal RP n=1600 | Optimal EBRT n=879 | Optimal EBRT+BT n=461 |
|---|---|---|---|---|---|---|
| ***Radical Prostatectomy Patients*** | | | | | | |
| Pathological T stage | | | | | | |
| 2 | 786 (25%) | n/a | n/a | 459 (29%) | n/a | n/a |
| 3a | 980 (31%) | | | 554 (35%) | | |
| 3b | 1331 (42%) | | | 561 (35%) | | |
| 4 | 65 (2%) | | | 25 (2%) | | |
| Treatment Effect | 13 (0%) | | | 1 (0%) | | |
| Pathological Gleason Grade Group | | | | | | |
| 1 | 46 (1%) | n/a | n/a | 33 (2%) | n/a | n/a |
| 2 | 629 (20%) | | | 466 (29%) | | |
| 3 | 981 (31%) | | | 578 (36%) | | |
| 4 | 312 (10%) | | | 178 (11%) | | |
| 5 | 1170 (37%) | | | 344 (22%) | | |
| Treatment Effect | 38 (1%) | | | 1 (0%) | | |
| Positive margins | 1370 (43%) | n/a | n/a | 654 (37%) | n/a | n/a |
| Positive lymph nodes | 1174 (37%) | n/a | n/a | 357 (20%) | n/a | n/a |
| RP alone | 1587 (50%) | | | 744 (47%) | | |
| Neoadjuvant systemic therapy alone | 275 (9%) | | | 77 (5%) | | |
| Adjuvant radiotherapy | 347 (11%) | | | 198 (12%) | | |
| Adjuvant systemic therapy alone | 120 (4%) | | | 70 (4%) | | |
| Salvage radiotherapy | 847 (27%) | | | 511 (32%) | | |
| ***Radiotherapy Patients*** | | | | | | |
| Upfront androgen deprivation therapy usage | | 1395 (76%) | 897 (90%) | | 879 (100%) | 420 (100%) |
| Duration of androgen deprivation therapy, median (IQR) (months) | | 22 (12-30) | 12 (4-24) | | 28 (24-36) | 24 (18-24) |
| Brachytherapy type | | | | | | |
| Low dose rate | | | 353 (35%) | | | 72 (16%) |
| High dose rate | | | 646 (65%) | | | 389 (84%) |
| ***All Patients*** | | | | | | |
| Local salvage | 847 (27%) | 18 (1%) | 4 (0%) | 511 (34%) | 8 (1%) | 0 (0%) |
| Systemic salvage | 468 (15%) | 319 (17%) | 93 (9%) | 215 (14%) | 150 (17%) | 15 (3%) |

EBRT, external beam radiotherapy; EBRT+BT, external beam radiotherapy with brachytherapy boost; n, number; RP, radical prostatectomy

**eTable 3.** Specific Breakdown of Presence of Adverse Clinicopathologic Features by Cohort

| Characteristic | All RP n=3175 | All EBRT n=1830 | All EBRT+BT n=999 | Optimal RP n=1600 | Optimal EBRT n=879 | Optimal EBRT+BT n=461 |
|---|---|---|---|---|---|---|
| Primary Gleason Pattern 5 | 600 (19%) | 166 (9.1%) | 165 (18.2%) | 123 (7.7%) | 78 (8.9%) | 60 (15.7%) |
| 50% percent cores positive | 2398 (89.5%) | 1467 (89%) | 558 (80.9%) | 1276 (91.6%) | 707 (86.4%) | 219 (85.5%) |
| cT3b-4 | 154 (5%) | 308 (17%) | 135 (13.6%) | 84 (5.4%) | 176 (20.3%) | 62 (13.5%) |
| ≥2 NCCN High risk features | 2264 (71.3%) | 1035 (56.6%) | 459 (45.9%) | 1191 (74.4%) | 458 (52.1%) | 178 (38.6%) |
| Multiple unfavorable features in one patients | 338 (10.6%) | 281 (15.4%) | 146 (14.6%) | 82 (5.1%) | 159 (18.1%) | 61 (13.2%) |
| Unfavorable by | | | | | | |
| ≥2 NCCN High risk features only | 368 (11.6%) | 189 (10.3%) | 304 (30.4%) | 200 (12.5%) | 90 (10.2%) | 191 (41.4%) |
| Other features only | 2264 (71.3%) | 1035 (56.6%) | 459 (45.9%) | 1191 (74.4%) | 458 (52.1%) | 178 (38.6%) |
| Both | 543 (17.1%) | 606 (33.1%) | 236 (23.6%) | 209 (13.1%) | 331 (37.7%) | 92 (20%) |

EBRT, external beam radiotherapy; EBRT+BT, external beam radiotherapy with brachytherapy boost; n, number; NCCN, National Comprehensive Cancer Network; RP, radical prostatectomy

The percentages in any individual characteristics may add up to >100%, as any given patient may have more than 1 unfavorable risk characteristic.

**eTable 4.** Covariate Effect Sizes Before and After Inverse Probability of Treatment Weighting Across Treatment Groups

| Parameter | All patients | | Appropriate Multimodality Treatment | |
|---|---|---|---|---|
| | Unweighted Effect size | Weighted Effect Size | Unweighted Effect size | Weighted Effect Size |
| Age | 0.23 | 0.16 | 0.23 | 0.14 |
| Initial PSA | 0.15 | 0.08 | 0.18 | 0.14 |
| Biopsy Gleason Grade Group | 0.12 | 0.05 | 0.08 | 0.05 |
| Clinical Tumor Stage | 0.30 | 0.29 | 0.37 | 0.35 |

Effect sizes were determined using the partial eta-squared method before and after inverse probability of treatment weighting. Inverse probability of treatment weights were calculated using propensity scores that were determined using multinomial logistic regression with treatment cohort as the outcome and the presence of unfavorable disease (yes/no) and site-centered age at treatment, ln(initial PSA), clinical T stage, Gleason Grade group as pre-treatment prognostic covariates.

**eTable 5.** Clinical Characteristics After Propensity Score Adjustment

| | All RP (3261.8) | All EBRT (1678.3 ) | All EBRT + BT (955.5) | p-value | Optimal RP (1781.3) | Optimal EBRT (750.9) | Optimal EBRT + BT (350.7) | p-value |
|---|---|---|---|---|---|---|---|---|
| Median Follow-up (IQR) | 3.82 (2.07-6.21) | 6.78 (3.99-10.21) | 7.22 (4.23-9.92) | <0.001 | 3.99 (2.09-6.41) | 7.28 (4.49-10.61) | 8.02 (5.87-10.56) | <0.001 |
| Age, median (IQR) (years) | 65.3 (59.6-70) | 67 (60-73) | 68 (62.2-74) | <0.001 | 65.4 (60-70) | 68 (61.9-74) | 67 (62-72.1) | <0.001 |
| Initial PSA, median (IQR) (ng/mL) | 13.4 (6.3-28) | 14 (6.8-28.7) | 17.4 (8-29.8) | 0.005 | 12 (6.4-27.4) | 14.1 (6.8-31.2) | 21.4 (10.3-34) | 0.6 |
| Biopsy Gleason Grade Group | | | | <0.001 | | | | <0.001 |
| 1 | 214.6 (6.6%) | 47.5 (2.8%) | 65.2 (6.8%) | | 98.5 (5.5%) | 26.2 (3.5%) | 36.9 (10.5%) | |
| 2 | 351.4 (10.8%) | 168.6 (10.1%) | 76.2 (8%) | | 180.6 (10.1%) | 80.3 (10.7%) | 35.2 (10%) | |
| 3 | 353 (10.8%) | 146.7 (8.7%) | 139.9 (14.6%) | | 190.6 (10.7%) | 66.6 (8.9%) | 75.2 (21.4%) | |
| 4 | 1414 (43.4%) | 747.1 (44.5%) | 338.2 (35.4%) | | 1155.3 (64.9%) | 324.7 (43.3%) | 103.1 (29.4%) | |
| 5 | 928.7 (28.5%) | 568.4 (33.9%) | 335.9 (35.2%) | | 156.4 (8.8%) | 253 (33.7%) | 100.3 (28.6%) | |
| Clinical Tumor Category (%) | | | | <0.001 | | | | <0.001 |
| 1c | 1488.8 (45.6%) | 489.2 (29.2%) | 197.1 (20.6%) | | 843.5 (47.4%) | 204.5 (27.2%) | 60.6 (17.3%) | |
| 2a | 580.4 (17.8%) | 274.1 (16.3%) | 82.3 (8.6%) | | 347.9 (19.5%) | 122.8 (16.4%) | 24.7 (7%) | |
| 2b | 443.7 (13.6%) | 230.9 (13.8%) | 134.1 (14%) | | 222.3 (12.5%) | 108.4 (14.4%) | 27.7 (7.9%) | |
| 2c | 249.6 (7.7%) | 152.4 (9.1%) | 110.7 (11.6%) | | 102.4 (5.8%) | 65.1 (8.7%) | 48.6 (13.9%) | |
| 3a | 339.1 (10.4%) | 275 (16.4%) | 285.2 (29.9%) | | 180.9 (10.2%) | 134.7 (17.9%) | 132.1 (37.7%) | |
| 3b | 143.7 (4.4%) | 199.8 (11.9%) | 125.3 (13.1%) | | 75.6 (4.2%) | 93.8 (12.5%) | 51.4 (14.7%) | |
| 4 | 16.5 (0.5%) | 56.8 (3.4%) | 20.9 (2.2%) | | 8.8 (0.5%) | 21.5 (2.9%) | 5.6 (1.6%) | |

EBRT, external beam radiotherapy; EBRT+BT, external beam radiotherapy with brachytherapy boost; IQR, interquartile range; RP, radical prostatectomy; Continuous variables across treatments are compared using Kruskal-Wallis test. The association between treatment and categorical variables are assessed using chi-square test of association

**eTable 6.** Cause-Specific Regression Models of Time Until Prostate Cancer-Specific Mortality and Distant Metastasis

| | Hazard Ratio (95%CI) | p-value |
|---|---|---|
| **All Patients with Unfavorable Disease** | | |
| **Prostate Cancer Specific Mortality** | | |
| All EBRT *versus* All RP | **0.73 (0.59-0.91)** | **0.006** |
| All EBRT+BT *versus* All RP | **0.65 (0.49-0.86)** | **0.003** |
| All EBRT+BT *versus* All EBRT | 0.89 (0.67-1.18) | 0.418 |
| **Distant Metastasis** | | |
| All EBRT *versus* All RP | **0.5 (0.44-0.58)** | **<0.001** |
| All EBRT+BT *versus* All RP | **0.29 (0.23-0.36)** | **<0.001** |
| All EBRT+BT *versus* All EBRT | **0.58 (0.46-0.73)** | **<0.001** |
| **Optimally Treated Men with Unfavorable Disease** | | |
| **Prostate Cancer Specific Mortality** | | |
| Optimal EBRT *versus* Optimal RP | 0.69 (0.47-1.01) | 0.054 |
| Optimal EBRT+BT *versus* Optimal RP | 0.77 (0.47-1.25) | 0.288 |
| Optimal EBRT+BT *versus* Optimal EBRT | 1.12 (0.68-1.83) | 0.653 |
| **Distant Metastasis** | | |
| Optimal EBRT *versus* Optimal RP | **0.48 (0.38-0.61)** | **<0.001** |
| Optimal EBRT+BT *versus* Optimal RP | **0.25 (0.17-0.38)** | **<0.001** |
| Optimal EBRT+BT *versus* Optimal EBRT | **0.52 (0.34-0.81)** | **0.003** |

CI, confidence interval; EBRT, external beam radiotherapy; EBRT+BT, external beam radiotherapy with brachytherapy boost; RP, radical prostatectomy

Models are adjusted for sites as random effect with inverse probability of treatment weights, calculated using propensity scores that were determined using multinomial logistic regression with treatment cohort as the outcome and the presence of unfavorable disease (yes/no) and site-centered age at treatment, ln(initial PSA), clinical T stage, Gleason Grade group as pre-treatment prognostic covariates. These models are doubly robust (i.e., were also adjusted for each of those covariates including the propensity score calculation).

**eTable 7.** Cause-Specific Regression Models of Time Until All-Cause Mortality

| | **Hazard Ratio & 95%CI** | **p-value** |
|---|---|---|
| **All Patients with Unfavorable Disease** | | |
| **All EBRT versus All RP** | **0.77 (0.68-0.87)** | **<0.001** |
| **All EBRT+BT versus All RP** | **0.84 (0.73-0.97)** | **0.016** |
| All EBRT+BT versus All EBRT | 1.1 (0.95-1.27) | 0.225 |
| **Optimally Treated Men with Unfavorable Disease** | | |
| **Optimal EBRT versus Optimal RP** | **0.56 (0.46-0.68)** | **<0.001** |
| Optimal EBRT+BT versus Optimal RP | **0.75 (0.6-0.94)** | **0.012** |
| Optimal EBRT+BT versus Optimal EBRT | **1.34 (1.05-1.69)** | **0.016** |

CI, confidence interval. EBRT, external beam radiotherapy; EBRT+BT, external beam radiotherapy with brachytherapy boost; RP, radical prostatectomy

Models are adjusted for sites as random effect with inverse probability of treatment weights, calculated using propensity scores that were determined using multinomial logistic regression with treatment cohort as the outcome and the presence of unfavorable disease (yes/no) and site-centered age at treatment, ln(initial PSA), clinical T stage, Gleason Grade group as pre-treatment prognostic covariates. These models are doubly robust (i.e., were also adjusted for each of those covariates including the propensity score calculation). Note that proportional hazards were not met.