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**Supplementary Statistical Methods**

A Network Meta-Analysis approach was adopted for pair-wise meta-analysis of treatments.1,2 Fixed-effect and random-effects models were adopted after evaluating the heterogeneity and inconsistency of the included studies by between-studies variance, percentage of the total variability in a set of effect sizes due to true heterogeneity, and Q test for heterogeneity/inconsistency, and treatments were ranked by P-score, a frequentist analogue to the surface under the cumulative ranking curve. A standard meta-analysis was performed to compare outcomes between Gleason grade group (GG) 5 and GG 4 disease as a function of androgen deprivation therapy (ADT) duration. All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc. 2013) and Packages “netmeta” (Network Meta-Analysis using Frequentist Methods) and “meta” in the R statistical software environment version 3.3.1.3

For all Markov proportional hazard (PH) models, the covariates GG and ADT treatment group were included as transition-specific covariates due to their association with our outcomes of interest.2 To avoid over-parameterization, the covariates T-stage and age were included as covariates with homogeneous effects across transitions. Specifically, for the Markov PH model for prostate cancer-specific survival, the inclusion of T-stage induced instability and was therefore dropped. For the three-state multi-state model, the transition hazards for the transition into the distant metastasis (DM) or death either the relapse-free state or from the local failure (LF) state are assumed to be proportional. Further, transition from relapse-free to the LF state is considered to be in one stratum and transitions to the DM or death state are considered to be in another stratum. To distinguish transitions to the DM or death state from the relapse-free state or LF state, a time-dependent covariate, indicating whether or not LF has occurred or not, was introduced. That is, for transitions from the relapse-free state, the value of this LF covariate equals 0 as the DM or death state is entered directly, while for patients transitioning from the LF state, the value of this LF covariate equals to 1 as the DM or death state is entered from the LF state.

**Supplementary Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses Flowchart**

Records excluded  
(n = 123)

Full-text articles excluded due to unavailability of individual patient data  
(n = 19)

Records after duplicates removed  
(n = 148)

Records screened  
(n = 148)

Data sharing applications submitted to RTOG and EORTC

Randomized trials with available individual patient data  
(n = 6)

Records identified through database searching  
(n = 1043)

Full-text articles assessed for eligibility  
(n = 25)

## Identification

## Eligibility

## Included

## Screening

**Supplementary Figure 2. Crude Incidences of Transitions in Four-State Model**

**RT alone**

Relapse-Free

(State 1)

Local Failure

(State 2)

Distant Metastasis

(State 3)

Death

(State 4)

58

(24%)

95

(40%)

45

(19%)

27

(11%)

21

(9%)

112

(47%)

239

Relapse-Free

(State 1)

Local Failure

(State 2)

Distant Metastasis

(State 3)

Death

(State 4)

75

(21%)

93

(25%)

94

(26%)

34

(9%)

25

(7%)

115

(32%)

365

**RT + STADT**

Relapse-Free

(State 1)

Local Failure

(State 2)

Distant Metastasis

(State 3)

Death

(State 4)

13 (12%)

34

(31%)

37

(34%)

4

(4%)

7

(6%)

32

(30%)

108

Relapse-Free

(State 1)

Local Failure

(State 2)

Distant Metastasis

(State 3)

Death

(State 4)

34 (12%)

51

(18%)

101 (36%)

12

(4%)

16

(6%)

56

(20%)

280

**RT + LTADT**

**RT + Lifelong ADT**

**Supplementary Figure 3. Crude Incidences of Transitions in Three-State Model**

Relapse-Free

(State 1)

Local Failure

(State 2)

Distant Metastasis or Death

(State 3)

58

(24%)

140

(59%)

239

**RT alone**

**RT + STADT**

**RT + LTADT**

**RT + Lifelong ADT**

Relapse-Free

(State 1)

Local Failure

(State 2)

Distant Metastasis or Death

(State 3)

75

(21%)

187

(51%)

365

Relapse-Free

(State 1)

Local Failure

(State 2)

Distant Metastasis or Death

(State 3)

34

(12%)

152

(54%)

280

Relapse-Free

(State 1)

Local Failure

(State 2)

Distant Metastasis or Death

(State 3)

13

(12%)

71

(66%)

108

48

(20%)

59

(16%)

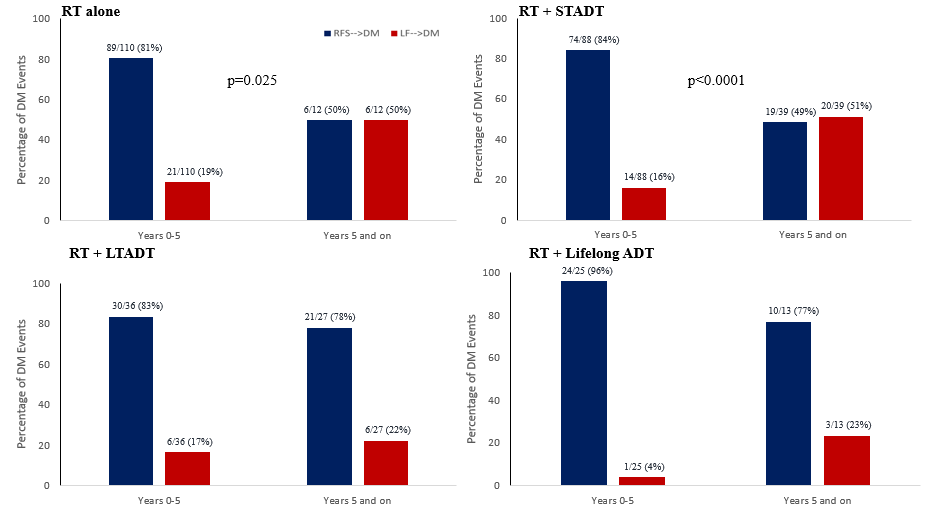
28

(10%)

11

(10%)

**Supplementary Figure 4. Proportion of Metastases Arising from Relapse Free State and Local Failure State over Time**



**Supplementary Table 1. Summary of Trials Included in Meta-Analysis**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Trial** | **Arms** | **Inclusion\*** | **Staging Workup** | **Primary Endpoint** | **ADT Regimen** | **RT Dose** |
| ROTG 8531 | RT vs RT+Lifelong ADT | cT1-T2N+ or cT3-4 <25 cm2\*\* | Bone scan, chest x-ray; lymph node assessment by lymphangiogram, CT, or lymph node sampling | Survival and disease progression | q1month LHRH agonist | 65-70 Gy to prostate  44-46 Gy to pelvis |
| RTOG 8610 | RT vs RT+ STADT | cT2-T4 ≥25 cm2 | Bone scan, chest x-ray; lymph node assessment by lymphangiogram, CT, or lymph node sampling | Locoregional control | q1month LHRH agonist + 4 months AA | 65-70 Gy to prostate  44-46 Gy to pelvis |
| RTOG 9202 | RT+STADT vs RT+LTADT | cT2-4N0-X, PSA<150 | Bone scan, chest x-ray; lymph node assessment by lymphangiogram, CT, or lymph node sampling | Disease free survival | Q1month LHRH agonist + 4 months AA | 65-70 Gy to prostate  44-46 Gy to pelvis |
| EORTC 22863 | RT vs RT + LTADT | cT1-2N0 WHO grade 3  cT3-4N0 | Bone scan, chest X-ray, liver ultrasound or CT; allowed lymph node assessment by CT, bipedal lymphangiography, lymphadenectomy | Disease free survival | q1month LHRH agonist + 1 month AA | 70 Gy to prostate  50 Gy to pelvis |
| EORTC 22961 | RT+STADT vs RT+LTADT | cT1c-2bN+  cT3-4N0  PSA<40xULN | Bone scan, chest X-ray, CT or MRI of abdomen and pelvis; lymphadenectomy allowed | Overall survival | q1-3 month LHRH agonist + 6 mos AA | 70 Gy to prostate  50 Gy to pelvis |
| EORTC 22991 | RT vs RT+ STADT | cT1b-c, with PSA≥ 10 ng/mL or Gleason ≥ 7  cT2a with PSA≤50 | Bone scan for PSA>10 ng/mL, chest x-ray, CT or MRI of abdomen and pelvis | Biochemical disease free survival | q3month LHRH agonist + 1 month AA | 70-78 Gy to prostate  46 Gy to pelvis |

AA, anti-androgen; ADT, androgen deprivation therapy; CT, computed tomography; LHRH, luteinizing hormone releasing hormone; LTADT, long term ADT; MRI, magnetic resonance imaging; RT, radiation therapy; STADT, short-term ADT

\*Patients with cN+ or pN+ disease were included on several protocols, but were not included in our analysis.

\*\*RTOG 8531 also included patients with high-risk features after radical prostatectomy, who were not included in our analysis.

**Supplementary Table 2. Crude Event Incidence for Metastases, Prostate Cancer-Specific Mortality, and All-Cause Mortality**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **GG 4** | | | | | **GG 5** | | | | |
| **Trial** | **Arm** | **Total** | **#LF** | **#DM** | **#PCSM** | **#ACM** | **Total** | **#LF** | **#DM** | **#PCM** | **#ACM** |
| **RTOG 8531** | RT Alone | 61 | 27 | 33 | 23 | 49 | 47 | 47 | 32 | 25 | 41 |
| Lifelong ADT | 59 | 15 | 25 | 17 | 38 | 49 | 49 | 16 | 12 | 38 |
| **RTOG 8610** | RT Alone | 33 | 12 | 20 | 16 | 27 | 36 | 36 | 24 | 25 | 30 |
| STADT | 29 | 13 | 14 | 12 | 25 | 30 | 30 | 17 | 16 | 25 |
| **RTOG 9202** | STADT | 93 | 28 | 38 | 36 | 79 | 78 | 78 | 34 | 27 | 64 |
| LTADT | 92 | 14 | 19 | 20 | 79 | 74 | 74 | 24 | 20 | 60 |
| **EORTC 22863** | RT Alone | 17 | 7 | 11 | 8 | 13 | 7 | 7 | 6 | 4 | 4 |
| LTADT | 13 | 0 | 3 | 2 | 5 | 6 | 6 | 0 | 0 | 2 |
| **EORTC 22961** | STADT | 56 | 7 | 9 | 3 | 18 | 34 | 34 | 16 | 9 | 15 |
| LTADT | 75 | 8 | 14 | 9 | 21 | 21 | 21 | 5 | 3 | 6 |
| **EORTC 22991** | RT Alone | 29 | 3 | 3 | 2 | 10 | 8 | 8 | 3 | 3 | 4 |
| STADT | 36 | 2 | 2 | 2 | 6 | 9 | 9 | 3 | 2 | 2 |
|  | | **GG 4** | | | | | **GG 5** | | | | |
| **Total** | **#LF** | **#DM** | **#PCSM** | **#ACM** | **Total** | **#LF** | **#DM** | **#PCM** | **#ACM** |
| **Total** | | **593** | **136** | **191** | **150** | **370** | **399** | **105** | **180** | **146** | **291** |
| **Event Rate** | |  | **23%** | **32%** | **25%** | **62%** |  | **26%** | **45%** | **37%** | **73%** |

#ACM, number of all-cause mortality events; #DM, number of distant metastases; #PCSM, number of prostate cancer-specific mortality events; ADT, androgen deprivation therapy; GG, Gleason grade group; LF; local failure; LTADT, long term ADT; RT, radiation therapy; STADT, short-term ADT

**Supplementary Table 3. Baseline Patient Characteristics**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Overall** | **GG 4** | **GG 5** |
| **Age median (interquartile range )**  **(years)** | 70  (66-74) | 70  (66-74) | 71  (67-75) |
| **Initial PSA,median**  **(interquartile range)**  **(ng/dL)\*** | 18.8  (10-39.8) | 18.62  (9.7-39.5) | 18.9  (10.8-40.3) |
| **Clinical Tumor Stage** |  |  |  |
| 1 | 48 (5%) | 35 (6%) | 13 (3%) |
| 2 | 270 (27%) | 175 (29%) | 95 (24%) |
| 3 | 636 (64%) | 368 (62%) | 268 (67%) |
| 4 | 38 (4%) | 15 (3%) | 23 (6%) |

GG, Gleason grade group

\*Initial PSA not available for RTOG 8531 and EORTC 22961, and only available for some patients on RTOG 8610, EORTC 22863, and EORTC 22991

**Supplementary Table 4. Cumulative Incidences of Local Failure and Distant Metastasis (with Death as a Competing Risk)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | 5-year estimates (95% CI) | | 7-year estimates (95% CI) | | 10-year estimates (95% CI) | |
|  | LF | DM | LF | DM | LF | DM |
| RT alone | | | | | | |
| GG 4 | 25% (18-32%) | 40% (32%-48%) | 27% (19-34%) | 45% (36%-53%) | 33% (24-42%) | 45% (36%-53%) |
| GS 5 | 35% (25%-44%) | 58% (47%-68%) | 36% (26%-46%) | 58% (47%-68%) | 36% (26%-46%) | 60% (50%-70%) |
| RT+ STADT | | | | | | |
| GG 4 | 20% (14-25%) | 17% (12%-22%) | 23% (17%-28%) | 24% (18%-30%) | 23% (18%-29%) | 31% (24%-38%) |
| GS 5 | 16% (10-22%) | 35% (27%-42%) | 22% (15%-29%) | 41% (33%-49%) | 22% (15%-29%) | 44% (35%-52%) |
| RT+ LTADT | | | | | | |
| GG 4 | 7% (3-11%) | 9% (5-13%) | 11% (6%-16%) | 14% (8%-19%) | 13% (7%-18%) | 20% (13%-26%) |
| GS 5 | 13% (6%-20%) | 20% (12%-28%) | 14% (7%-21%) | 22% (14%-31%) | 14% (7-21%) | 31% (21%-42%) |
| RT + Lifelong ADT | | | | | | |
| GG 4 | 14% (5-23%) | 26% (15%-38%) | 19% (9%-30%) | 32% (19%-44%) | 21% (10%-32%) | 38% (25%-51%) |
| GS 5 | 8% (0-16%) | 20% (9%-32%) | 8% (0-16%) | 25% (12%-37%) | 13% (3%-23%) | 31% (18%-45%) |

ADT, androgen deprivation therapy; CI, confidence interval; DM, distant metastases; GG, Gleason grade group; LF; local failure; LTADT, long term ADT; RT, radiation therapy; STADT, short-term ADT

**Supplementary Table 5. Individual Study Cox Proportional Hazard Models for Local Failure**

|  |  |  |  |
| --- | --- | --- | --- |
| Study | **Local Failure** | | **ADT Treatment Group x GG Interaction Term** |
| GG 4 | GG 5 | p-value |
| RTOG 8531: Lifelong ADT vs RT alone | **0.36 (0.19-0.71)** | **0.19 (0.08-0.49)** | 0.3 |
| RTOG 8610: STADT vs RT alone | 0.93 (0.42-2.06) | 1.33 (0.66-2.67) | 0.5 |
| RTOG 9202: LTADT vs STADT | **0.45 (0.23-0.86)** | 0.75 (0.38-1.48) | 0.3 |
| EORTC 22863: LTADT vs RT alone | **(0-0)\*** | **(0-0)\*** | 1.00\* |
| EORTC 22961: LTADT vs STADT | 0.81 (0.28-2.36) | 0.44 (0.05-3.89) | 0.6 |
| EORTC 22991: STADT vs RT alone | 1.06 (0.07-17.48) | 1.01 (0.08-13.21) | 1.00 |

Note: HR of treatment difference is based on multivarable Cox Proportional Hazards regression adjusting for treatment, gleason score, treatment\*gleason score, age,and t stage

ADT, androgen deprivation therapy; GG, Gleason grade group; LTADT, long term ADT; RT, radiation therapy; STADT, short-term ADT

Hazard ratios are shown above, with 95% confidence intervals in parentheses.

\*The estimates from EORTC 22863 are unstable

**Supplementary Table 6. Network Meta-Analysis of Androgen Deprivation Therapy Duration on Local Progression**

|  |  |  |
| --- | --- | --- |
|  | **Local Failure** | |
| GG 4 | GG 5 |
| **RT Alone As Reference** | | |
| STADT | 0.67 (0.40, 1.13) | 1.68 (1.01, 2.79) |
| LTADT | **0.47 (0.26, 0.87)\*\*** | 1.21 (0.66, 2.24) |
| Lifelong ADT | **0.56 (0.37, 0.85)\*\*** | **0.43 (0.27, 0.66)\*\*** |
| **STADT as Reference** | | |
| LTADT | **0.71 (0.52, 0.96)\*\*** | 0.72 (0.51, 1.02) |
| Lifelong ADT | 0.83 (0.43, 1.64) | **0.25 (0.13, 0.50)\*\*** |
| **LTADT as Reference** | | |
| Lifelong ADT | 1.18 (0.56, 2.46) | **0.35 (0.16, 0.75)\*\*** |

ADT, androgen deprivation therapy; GG, Gleason grade group; LTADT, long term ADT; RT, radiation therapy; STADT, short-term ADT

Hazard ratios are shown above, with 95% confidence intervals in parentheses.

\*\* indicates p<0.05.

**Supplementary Table 7. Multivariable Cox Proportional Hazards Analyses with Local Failure as a Time-Dependent Variable**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **OS** | | **PCSS** | | **DMFS** | |
|  | HR (95% CI) | p-value | HR (95% CI) | p-value | HR (95% CI) | p-value |
| LF (time-dependent) | **1.7 (1.37, 2.1)** | **<0.001** | **3.1 (2.33, 4.12)** | **<0.001** | **1.92 (1.54, 2.39)** | **<0.001** |
| T3/4 vs. T1/2 | 1.17 (0.96, 1.41) | 0.11 | 1.14 (0.85, 1.53) | 0.4 | **1.25 (1.04, 1.51)** | **0.019** |
| Age (years) | **1.04 (1.02, 1.05)** | **<0.001** | 1 (0.98, 1.02) | 0.8 | **1.03 (1.02, 1.05)** | **<0.001** |
| GG 5 vs. GG 4 | 1.41 (0.88, 2.26) | 0.15 | **2.16 (1.09, 4.27)** | **0.028** | 1.54 (0.97, 2.46) | 0.068 |
| RT+STADT vs. RT alone | 0.7 (0.44, 1.1) | 0.12 | 0.69 (0.34, 1.37) | 0.3 | 0.69 (0.44, 1.08) | 0.11 |
| RT+LTADT vs. RT alone | **0.59 (0.37, 0.93)** | **0.024** | 0.5 (0.24, 1.03) | 0.060 | **0.6 (0.38, 0.94)** | **0.027** |
| RT+Lifelong ADT vs. RT alone | **0.65 (0.44, 0.97)** | **0.035** | **0.41 (0.21, 0.77)** | **<0.01** | **0.56 (0.37, 0.83)** | **<0.01** |
| GG 5 x RT+STADT | 1.02 (0.6, 1.76) | 0.9 | 0.84 (0.38, 1.85) | 0.7 | 1.02 (0.6, 1.74) | 1.0 |
| GG 5 x RT+LTADT | 0.84 (0.48, 1.48) | 0.6 | 0.65 (0.27, 1.55) | 0.3 | 0.78 (0.45, 1.35) | 0.4 |
| GG 5 x RT+ Lifelong ADT | \* | \* | \* | \* | \* | \* |

\*Estimate unavailable

ADT, androgen deprivation therapy; CI, confidence interval; DMFS, distant metastasis-free survival; GG, Gleason grade group; HR, hazard The estimates for interaction term (insignificant) between GG and ADT treatment arm are unlisted in the tableratio; LF; local failure; LTADT, long term ADT; OS, overall survival; PCSS, prostate cancer-specific survival; RT, radiation therapy; STADT, short-term ADT

Hazard ratios are shown above, with 95% confidence intervals in parentheses

**Supplementary Table 8. Multivariable Cox Proportional Hazards Analyses with Local Failure as a Time-Dependent Variable, Adjusted for Initial PSA (492 Patients)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **OS** | | **PCSS** | | **DMFS** | |
|  | HR (95% CI) | p-value | HR (95% CI) | p-value | HR (95% CI) | p-value |
| LF (time-dependent) | **1.42 (1.09, 1.86)** | **0.010** | **2.70 (1.85, 3.94)** | **<0.001** | **1.62 (1.23, 2.12)** | **<0.001** |
| GG 5 vs. GG 4 | 1.29 (0.66, 2.54) | 0.4 | 2.07 (0.84, 5.11) | 0.12 | 1.58 (0.75, 3.33) | 0.2 |
| RT+STADT vs. RT alone | 0.73 (0.45, 1.18) | 0.2 | 0.92 (0.43, 1.98) | 0.8 | 0.59 (0.26, 1.35) | 0.2 |
| RT+LTADT vs. RT alone | **0.59 (0.36, 0.96)** | **0.034** | 0.52 (0.23, 1.18) | 0.12 | 0.43 (0.18, 1.02) | 0.056 |
| RT+Lifelong ADT vs. RT alone | **--** | **--** | **--** | **--** | **--** | **--** |
| T3/4 vs T1/2 | 1.15 (0.92, 1.43) | 0.2 | 1.15 (0.80, 1.67) | 0.5 | 1.05 (0.83, 1.33) | 0.7 |
| Age (years) | **1.05 (1.03, 1.07)** | **<0.001** | 1.02 (0.99, 1.05) | 0.15 | **1.05 (1.03, 1.07)** | **<0.001** |
| iPSA (ng/mL) | 1.00 (1.00, 1.01) | 0.12 | **1.01 (1.00, 1.01)** | **0.032** | 1.00 (1.00, 1.01) | 0.15 |

ADT, androgen deprivation therapy; CI, confidence interval; DMFS, distant metastasis-free survival; GG, Gleason grade group; HR, hazard ratio; iPSA, initial PSA; LF; local failure; LTADT, long term ADT; OS, overall survival; PCSS, prostate cancer-specific survival; RT, radiation therapy; STADT, short-term ADT

Hazard ratios are shown above, with 95% confidence intervals in parentheses. Note, iPSA not available for patients enrolled on RTOG 8531, which is the only trial to examine lifelong ADT. Therefore, there are no estimates available for this subset of patients. The estimates for interaction term (insignificant) between GG and ADT treatment arm are unlisted in the table

**Supplementary Table 9. Hazard Rate Estimates in Patients with Local Control and Local Failure (as a Time-Independent Event)**

|  |  |  |
| --- | --- | --- |
| Time Interval (years) | Local Control | Local Failure |
| RT alone | | |
| 0-2 | 20 (14-25%) | 21 (13-29%) |
| 2-4 | 8 (4-12%) | 10 (4-17%) |
| 4-6 | 7 (2-12%) | 8 (1-14%) |
| 6-8 | 4 (0-8%) | 2 (0-6%) |
| 8-10 |  |  |
| RT+STADT | | |
| 0-2 | 7 (4%-9%) | 5 (1-8%) |
| 2-4 | 6 (4%-9%) | 10 (5-16%)) |
| 4-6 | 3 (1%-5%) | 5 (1-10%) |
| 6-8 | 3 (1%-6%) | 16 (6-26%) |
| 8-10 | 2 (0%-5%) | 9 (0-19%) |
| RT+LTADT | | |
| 0-2 | 2 (1-3%) | 1 (0-4%) |
| 2-4 | 3 (1-4%) | 3 (0-8%) |
| 4-6 | 5 (2-7%) | 6 (0-13%) |
| 6-8 | 3 (1-5%) | 9 (0-18%) |
| 8-10 | 2 (0-4%) | 10 (0-23%) |
| RT+Lifelong ADT | | |
| 0-2 | 6 (2-9%) | 6 (0-14%) |
| 2-4 | 7 (2-11%) | 7 (0-16%) |
| 4-6 | 3 (0-6%) | 4 (0-12%) |
| 6-8 | 5 (0-10%) | 25 (1-49%) |
| 8-10 | 2 (2-5%) |  |

ADT, androgen deprivation therapy; LTADT, long term ADT; RT, radiation therapy; STADT, short-term ADT

Hazard rates are shown above, with 95% confidence intervals in parentheses.

**Supplementary Table 10. Median Time to Distant Metastasis in Patients with Local Control versus Local Failure (as Time-Independent Event)**

|  |  |  |  |
| --- | --- | --- | --- |
| Treatment Stratum | Median Time to DM (years) | | p-value |
| LC | LF |
| RT | 1.41 | 1.83 | 0.3 |
| RT+STADT | 2.38 | 4.58 | <0.01 |
| RT+LTADT | 4.73 | 6.14 | 0.2 |
| RT+lifelong ADT | 2.82 | 5.35 | 0.19 |

ADT, androgen deprivation therapy; DM, distant metastases; LC, local control; LF, local failure; LTADT, long term ADT; RT, radiation therapy; STADT, short-term ADT

**Supplementary Table 11. Markov Proportional Hazards Models for Distant Metastasis-Free Survival in Three-State Model**

|  |  |  |
| --- | --- | --- |
|  | DMFS | |
|  | HR (95% CI) | p-value |
| Relative Hazards Between Specific Transitions | | |
| **LF->DMFS vs. RFS->DMFS** | **1.86 (1.03-3.36)** | **0.04** |
| Effect on the RFS->LF Transition | | |
| GG 5 vs GG 4 | 1.32 (0.91-1.90) | 0.14 |
| RT+ STADT vs RT Alone | 0.72 (0.44-1.19) | 0.2 |
| **RT+LTADT vs RT Alone** | **0.36 (0.20-0.63)** | **<0.001** |
| **RT+Lifelong ADT vs RT Alone** | **0.16 (0.05-0.45)** | **<0.001** |
| Effect on the RFS🡪DMFS Transition | | |
| **GG 5 vs GG 4** | **1.38 (1.12-1.71)** | **<0.01** |
| **RT+ STADT vs RT Alone** | **0.62 (0.43-0.90)** | **0.011** |
| **RT+LTADT vs RT Alone** | **0.45 (0.31-0.66)** | **<0.001** |
| **RT+Lifelong ADT vs RT Alone** | **0.43 (0.27-0.67)** | **<0.001** |
| Effect on the LF🡪DMFS Transition | | |
| GG 5 vs GG 4 | 0.90 (0.59-1.38) | 0.6 |
| RT+ STADT vs RT Alone | 0.71 (0.41-1.22) | 0.2 |
| RT+LTADT vs RT Alone | 0.59 (0.31-1.11) | 0.1 |
| RT+Lifelong ADT vs RT Alone | 0.93 (0.32-2.74) | 0.9 |
| Homogeneous Effect Across Transition | | |
| T3/T4 vs T1/T2 | 1.10 (0.92-1.31) | 0.3 |
| **Age** | **1.02 (1.01-1.03)** | **<0.001** |

ADT, androgen deprivation therapy; CI, confidence interval; DM, distant metastasis; DMFS, distant metastasis free survival; GG, Gleason grade group; HR, hazard ratio; LF; local failure; LTADT, long term ADT; OS, overall survival; PCSS, prostate cancer-specific survival; Ref, reference; RFS, relapse-free survival; RT, radiation therapy; STADT, short-term ADT. Hazard ratios are shown above, with 95% confidence intervals in parentheses.

**Supplementary Table 12. Brief Comparative Literature Overview of Series Examining the Relationship between Local Failure and Long-Term Outcomes**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Study | n | Study Period | Dose |  | ADT | Notes |
| Freiha 19844 | 64 | 1971-1977 | 70 Gy | 23.8% GG 4-5  48.6% ≥T3 | None | Of the 39 patients with a positive biopsy, 28 (71.2%) ultimately developed DMs and/or died of disease. Of the 25 with negative biopsies, only 6 (24%) ultimately developed DMs and/or died of disease. |
| Kuban 19875 | 286 | 1976-1984 | 62-65 Gy or I125 | 25.5% "poorly differentiated"  11.2% ≥T3 | None | Overall, 29% of patients treated with LDR and 14% of those treated with EBRT had LFs. Overall, DMs developed in 61% of those with LF versus 18% of those with LC (p=0.025). OS was significantly worse in patients with high-grade tumors who had LF (56%, versus 86% if locally controlled); p<0.05) |
| Fuks 19916 | 679 | 1970-1985 | LDR | 6% "poorly differentiated"  13% ≥T3 | None | Overall, 52% of patients had LFs.. The 15-year actuarial DMFS rate was 77% in those with LC versus 24% in those with LF (p<0.00001). The median DMFS was shorter in patients with LC than with those who had LR (p=0.0009). The annual incidence of DM also increased over time in patients with LF. |
| Zagars 19917 | 601 | 1965-1983 | 60-71 Gy | 10% grade 4 by MDACC grading  43% ≥T3 | None | Overall, 15% of patients had LFs. These patients had significantly shorter freedom from DM and worse PCSS than those with LC (p<0.001). When controlling for stage, grade, and other prognostic factors, DMs were significantly more frequent in patients with LF. |
| Coen 20028 | 1469 | 1972-1999 | 50-80 Gy, median 68.5 Gy | 69% GG 1; percent GG 4-5 not reported  37% ≥T3 | None | Overall, 13.4% of patients experienced LFs. When treated as a time-dependent variable, LF was a significant predictor of DMFS in Cox proportional hazard models (p=0.0001). DMFS was significantly diminished for patients with LF (p<0.0001), and the hazard rate of DM increased over time in patients with LF. Finally, among patients with DMs, the median time to DM was longer in patients with LF than in those with LC (p=0.0003). |
| Zelefsky 20089 | 339 | 1989-2001 | 72% had ≥75.6 Gy | 55% had GG 2-5; percent GG 4-5 not reported  22% ≥T3 | 39% STADT | Overall, 32% of patients had a positive biopsy. This was associated with a significantly lower DMFS than having a negative biopsy or a biopsy showing treatment effect (p=0.0004). This effect was also seen for PCSS (p=0.007). On multivariate analysis, a positive biopsy was a significant predictor of DM (p=0.003) and PCSM (p=0.014). |
| Current | 992 | 1987-2008 | 65-78, generally 70 Gy | 100% GG 4-5  68% T3-T4 | 24% no ADT  36.8% STADT  28.3% LTADT  10.9% lifelong | Overall, 24% of patients had LFs. When treated as a time-dependent variable, LF was a significant predictor of OS, PCSS, and DMFS in Cox proportional hazard models, accounting for the effect of GG, ADT treatment stratum, stage, and age. The hazard rate of DMs increased over time. Using a multi-state model analysis, the importance of the transition to a LF state on the outcomes of OS, PCSS, and DMFS were confirmed. The proportion of patients developing metastases subsequent to a local failure event increased significantly over time in patients treated with RT alone or RT+STADT. |

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