SUPPLEMENTARY MATERIALS

Supplementary Tables

Supplementary Figures

Tables

eTable 1. Selected Randomized Trials with Potentially Relevant Randomizations Excluded from the Meta-Analysis

Trial	Reason for Exclusion
RTOG 8531[1]	Used lifelong ADT duration in the experimental arm
Quebec L-101[2]	Did not report DM or OS
Quebec L-200[2]	Did not report DM or OS
Canada Multi-Center[3]	Did not report DM
Dana Farber Cancer Institute[4]	Did not report DM
MD Anderson[5]	Single-center
PROG 95-09[6]	Did not report DM
Harvard Proton Boost[7]	Single-center
Ontario[8]	Single-center
Mount Vernon[9]	Single-center
GETUG-08[10]	No IPD available
ASCENDE-RT[11]	No IPD available
PMH 9907[12]	Used only non-steroidal antiandrogen therapy
FLAME[13]	No IPD available

Abbreviations: ADT, androgen deprivation therapy; ASCENDE-RT, Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy; DM, distant metastasis; GETUG, Groupe d'Etudes des Tumeurs Uro-Génitales; IPD, individual patient data; PMH, Princess Margaret Hospital; PROG, Proton Radiation Oncology Group; OS, overall survival; RTOG, Radiation Therapy Oncology Group

eTable 2. Between-Trial Heterogeneity Assessment

Endpoint	tau^2	I^2	p value (test for homogeneity based on Q)
Metastasis-free survival	0.02	51.9%	0.01
Overall survival	0.01	28.2%	0.15
Biochemical recurrent-free survival	0.02	62.7%	0.001
Prostate cancer-specific mortality	0	0.0%	0.66
Other cause mortality	0.01	16.3%	0.28

eTable 3. Details on Androgen Deprivation Therapy (ADT) Dosing and Agents

Trial	ADT Details
RTOG 8610[14]	Goserelin s.c. monthly Flutamide 250 mg t.i.d for duration of ADT (4 months)
EORTC 22863[15]	Goserelin s.c. monthly cyproterone acetate 50 mg t.i.d. for 1 month
RTOG 9408[16]	Goserelin s.c. monthly or leuprolide i.m. monthly Flutamide 250 mg t.i.d for duration of ADT (4 months)
TROG 9601[17]	Goserelin s.c. monthly Flutamide 250 mg t.i.d for duration of ADT (3 or 6 months)
PCSIII[18]	Goserelin s.c. every 3 months Bicalutamide 50 mg daily for duration of ADT (6 months)
EORTC 22991[19]	Goserelin s.c. every 3 months Bicalutamide 50 mg daily for 1 month
RTOG 9202[20]	Goserelin s.c. monthly Flutamide 250 mg t.i.d for 4 months
EORTC 22961[21]	Triptorelin i.m. monthly (3/1/1998-7/15/1999), then triptorelin i.m. every 3 months Flutamide 250 mg t.i.d for 6 months
CKVO9610[22]	Luteinizing hormone-releasing hormone agonist (gosererlin or leuprolide) every 3 months cyproterone acetate 50 mg t.i.d. for 1 month
MRC RT01[23]	Goserelin s.c. monthly or leuprolide i.m. monthly cyproterone acetate 100 mg t.i.d or bicalutamide 50 mg daily for 1 month
DART/GICOR[24]	Goserelin s.c, x 1 month, then every 3 months Flutamide 250 mg t.i.d or bicalutamide 50 mg daily for 2 months
TROG RADAR[25]	Leuprorelin i.m. every 3 months

Abbreviations: ADT, androgen deprivation therapy; CKVO9610, Trial CKVO 9610 from the Dutch Cancer Society; DART/GICOR, DART trial from the Grupo de Investigación Clínica en Oncología Radioterápica; EORTC, European Organisation for Research and Treatment of Cancer; i.m., intramuscular; PCS, Prostate Cancer Study; RTOG, Radiation Therapy Oncology Group; s.c., subcutaneous; t.i.d., three times a day; TROG, Trans-Tasman Radiation Oncology Group

eTable 4. Eligible Patients by Trial, Stratified by Treatment Strategy

	Treatment Strategy					
	Low Dose RT	**Low Dose RT + STADT**	**Low Dose RT + LTADT**	**High Dose RT**	**High Dose RT + STADT**	**High Dose RT + LTADT**
RTOG 8610	**232**	**224**				
EORTC 22863	201		202			
RTOG 9202		727	729			
RTOG 9408	990	984				
TROG 9601	270	532*				
EORTC 22961		457	453			
CKVO9610	258	35	38	263	29	41
MRC RT01		421			422	
GICOR					176	176
PCSIII		200		200	200	
EORTC22991	100	101		309	309	
RTOG 0126	769			763		
TROG RADAR		279	273		247	252
Total	2820	3960	1695	1535	1383	469

Abbreviations: ADT, androgen deprivation therapy; CKVO9610, CKVO9610 trial from the Dutch Cancer Society; DART/GICOR, DART trial from the Grupo de Investigación Clínica en Oncología Radioterápica; EORTC, European Organisation for Research and Treatment of Cancer; LTADT, long-term ADT; MRC, MRC RT01, MRC RT01 trial from the Medical Research Council; PCS, Prostate Cancer Study; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group; STADT, short-term ADT; TROG, Trans-Tasman Radiation Oncology Group

eTable 5. Crude Event Rate Per Trial, Stratified by Treatment Strategy

Trial	Treatment Arm	Number of Patients	MFS Events	BCRFS Events	OS Events
RTOG 8610	Low Dose RT	232	193	*	184
	Low Dose RT + STADT	224	173	*	164
EORTC 22863	Low Dose RT	201	128	59*	108
	Low Dose RT + LTADT	202	84	92*	77
RTOG 9202	Low Dose RT + LTADT	729	576	633	571
	Low Dose RT + STADT	727	593	656	582
RTOG 9408	Low Dose RT	990	689	834	678
	Low Dose RT + STADT	984	672	773	657
TROG 9601	Low Dose RT	270	165	236	136
	Low Dose RT + STADT**	532	236	367	198
EORTC 22961	Low Dose RT + LTADT	453	104	132	90
	Low Dose RT + STADT	457	160	236	123
CKVO9610	Low Dose RT	258	88	168	80
	Low Dose RT + STADT	35	13	24	12
	Low Dose RT + LTADT	38	11	23	9
	High Dose RT	263	90	154	78
	High Dose RT + STADT	29	13	19	12
	High Dose RT + LTADT	41	16	21	14
MRC RT01	Low Dose RT + STADT	421	135	259	118
	High Dose RT + STADT	422	136	218	118
GICOR	High Dose RT+LTADT	176	14	20	10
	High Dose RT+STADT	176	33	38	27
PCSIII	Low Dose RT+STADT	200	88	104	85
	High Dose RT	200	94	117	91
	High Dose RT+STADT	200	84	99	82
EORTC22991	High Dose RT	309	116	180	107
	High Dose RT+STADT	309	97	128	88
	Low Dose RT	100	47	70	45
	Low Dose RT + STADT	101	48	59	47
RTOG 0126	High Dose RT	763	230	328	213

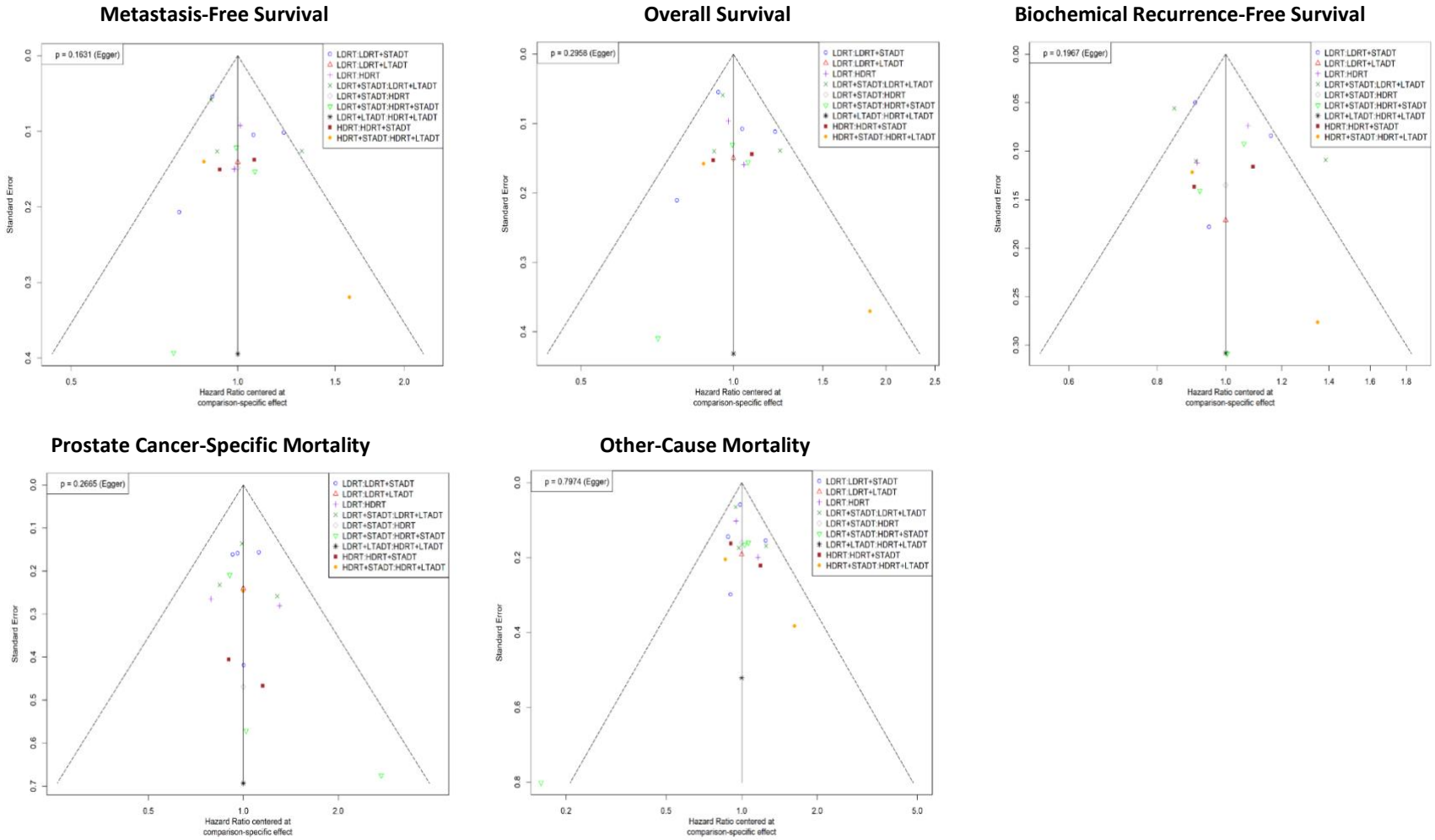
	Low Dose RT	769	239	421	218
TROG RADAR	High Dose RT+LTADT	252	93	125	72
	High Dose RT+STADT	247	113	147	91
	Low Dose RT + LTADT	273	117	151	99
	Low Dose RT + STADT	279	134	185	106

*BCRFS data not available for any patient enrolled on RTOG 8610, and only available for some patients enrolled on EORTC 22863
**Patients enrolled on the arms of TROG 9601 that included 3 and 6 months of ADT were categorized as receiving low dose RT + STADT in this analysis.

Abbreviations: ADT, androgen deprivation therapy; BCRFS, biochemical recurrence-free survival; CKVO9610, CKVO9610 trial from the Dutch Cancer Society; DART/GICOR, DART trial from the Grupo de Investigación Clínica en Oncología Radioterápica; EORTC, European Organisation for Research and Treatment of Cancer; LTADT, long-term ADT; MFS, metastasis-free survival; MRC, MRC RT01, MRC RT01 trial from the Medical Research Council; OS, overall survival; PCS, Prostate Cancer Study; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group; STADT, short-term ADT; TROG, Trans-Tasman Radiation Oncology Group

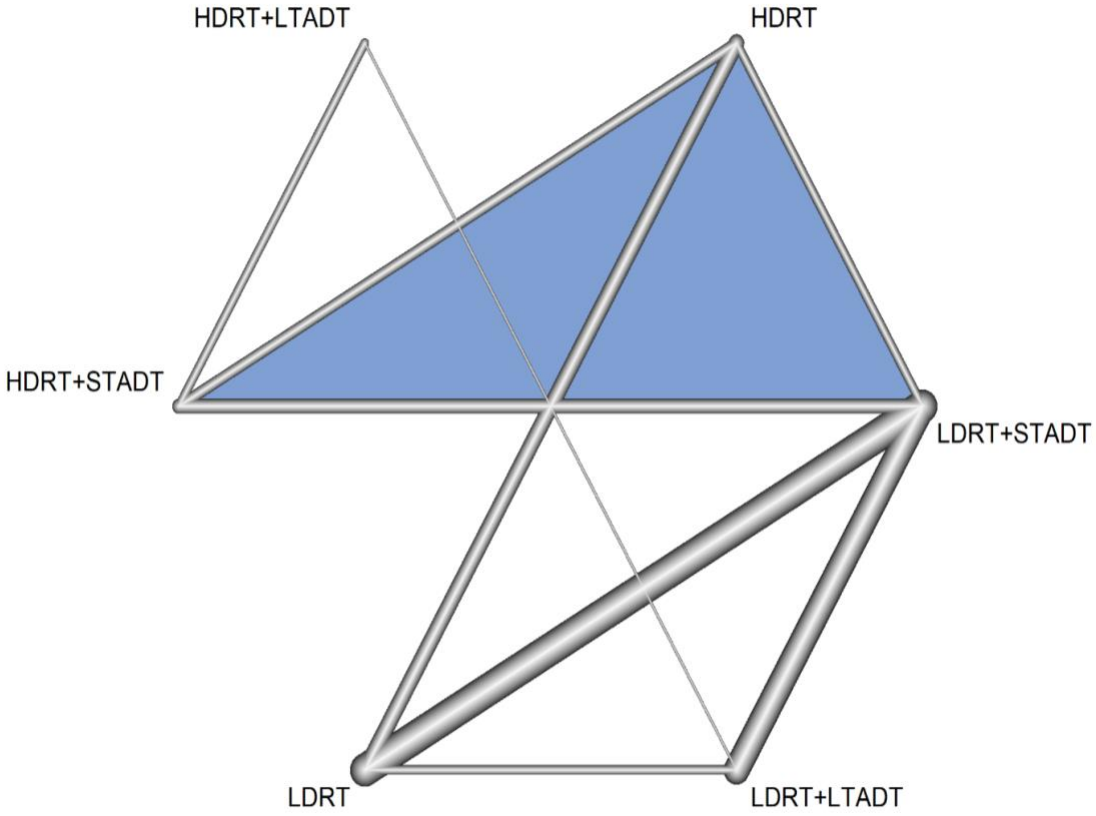
Supplementary Figures

eFigure 1. Funnel plots for publication bias for metastasis-free survival, overall survival, biochemical recurrence-free survival, prostate cancer-specific mortality, and other-cause mortality.

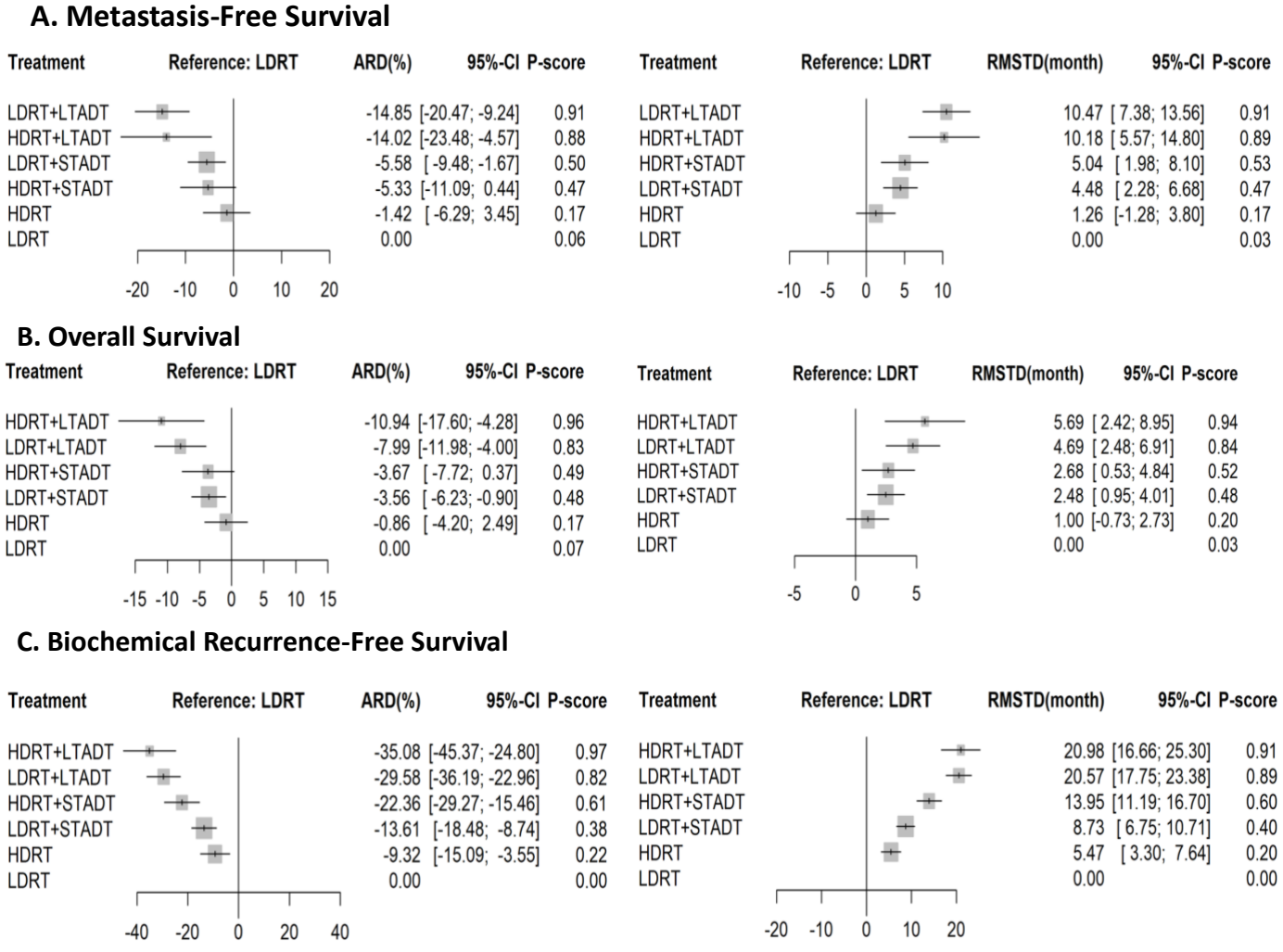


HDRT, high dose radiotherapy; LDRT, low dose radiotherapy; LTADT, long-term androgen deprivation therapy; STADT, short-term androgen deprivation therapy

eFigure 2. Network Plot of Randomized Trials with Available Direct Comparisons. Lines represent the presence of direct comparison trial(s). The width of the line is proportional to the number of trials with direct comparisons. HDRT, high dose radiotherapy; LDRT, low dose radiotherapy; LTADT, long term androgen deprivation therapy; STADT, short term androgen deprivation therapy. The shaded triangle represents the Prostate Cancer Study III trial, which had three arms that could be classified as distinct treatment strategies (LDRT+STADT, HDRT, and HDRT+STADT).

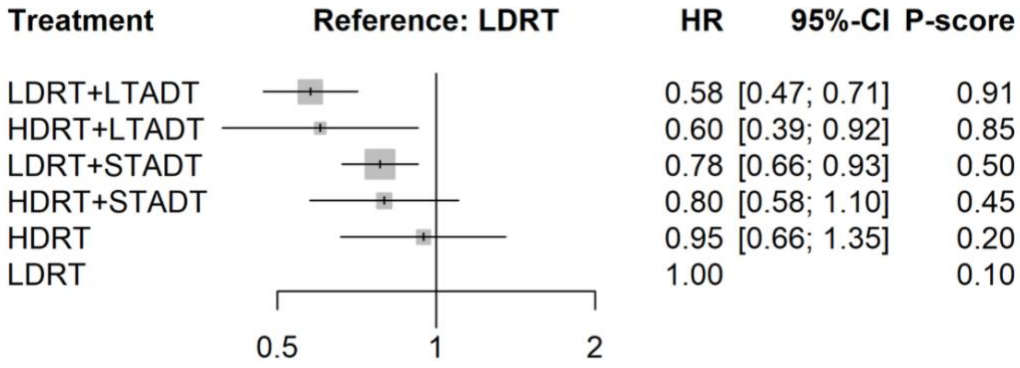


eFigure 3. Forest Plot Derived from Frequentist Network Meta-Analysis of Treatment Strategy Impact on Survival Outcomes. Note that the reference value (ARD and RMTSD) for each forest plot is low dose radiation therapy (LDRT) alone. For both 8-year absolute risk differences (ARDs) and restricted mean survival time differences (RMSTDs), estimates and their 95%confidence intervals (95%CI) are presented with the associated P-score (a frequentist analog to the surface under the cumulative ranking curve) presented at the far right. HDRT, high dose radiotherapy; LTADT, long term androgen deprivation therapy; STADT, short term androgen deprivation therapy.

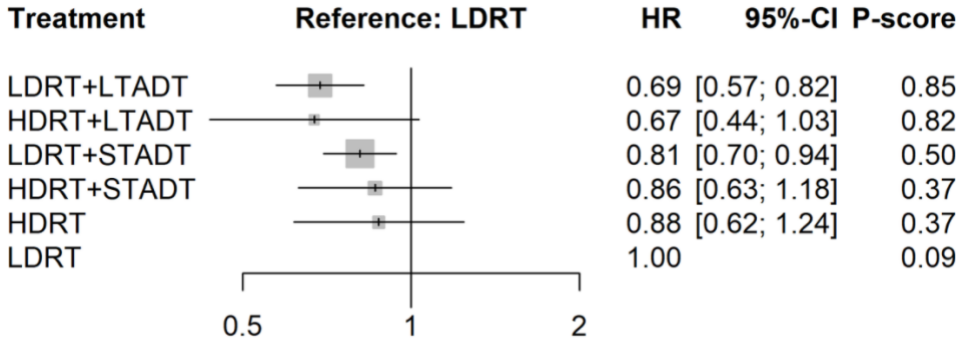


eFigure 4. Associations between Treatment Strategy and Outcomes for Patients with National Comprehensive Cancer Network (NCCN) High-Risk Disease. Note that the reference value (HR 1.00) for each forest plot is low dose radiation therapy (LDRT) alone. The hazard ratios (HRs) and 95%confidence intervals (95%CI) are presented with the associated P-score (a frequentist analog to the surface under the cumulative ranking curve) presented at the far right. HDRT, high dose radiotherapy; LTADT, long term androgen deprivation therapy; STADT, short term androgen deprivation therapy.

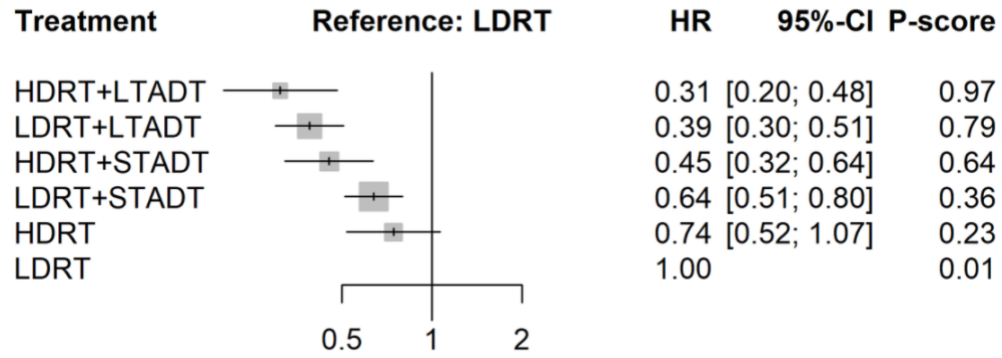
A. Metastasis-Free Survival



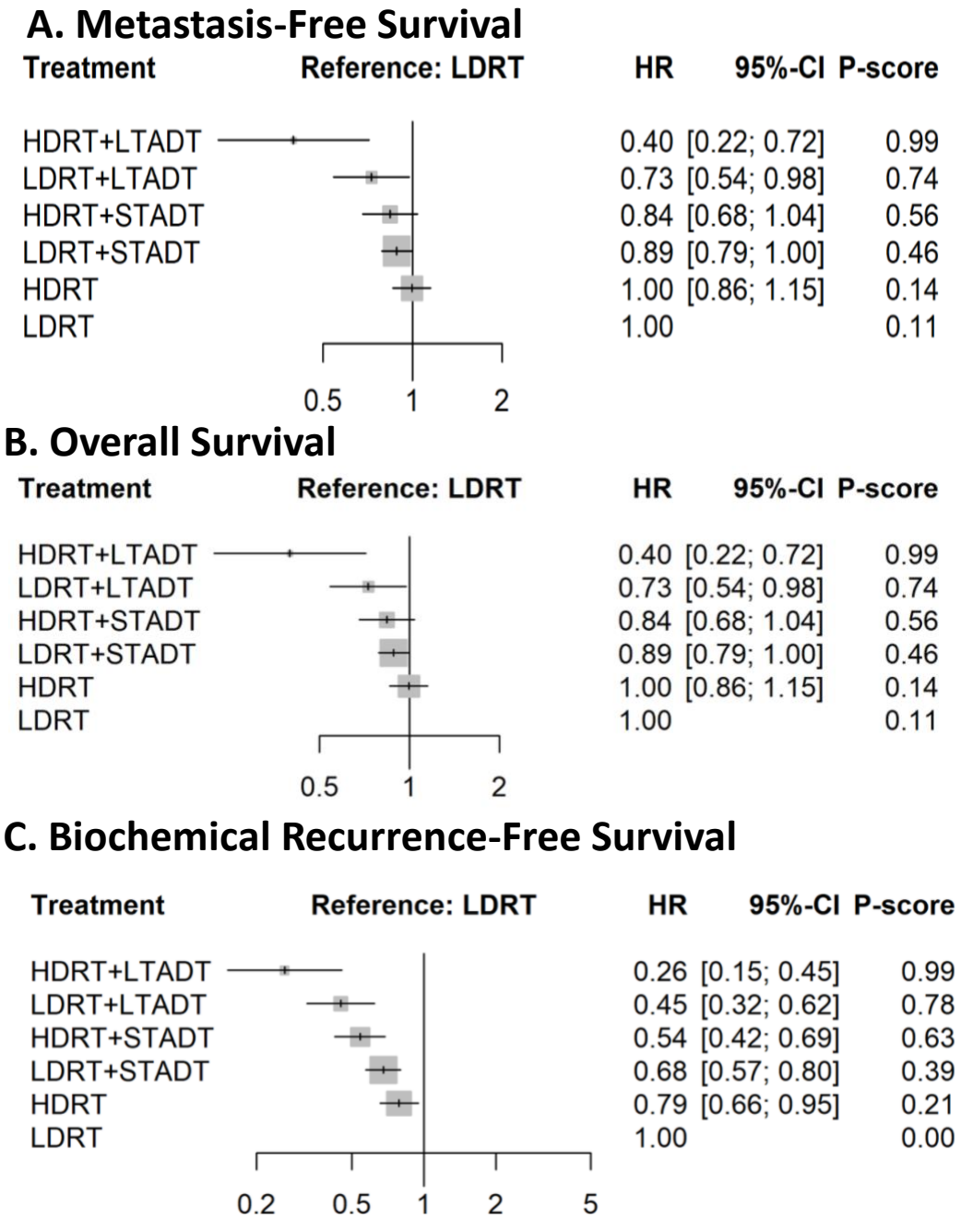
B. Overall Survival



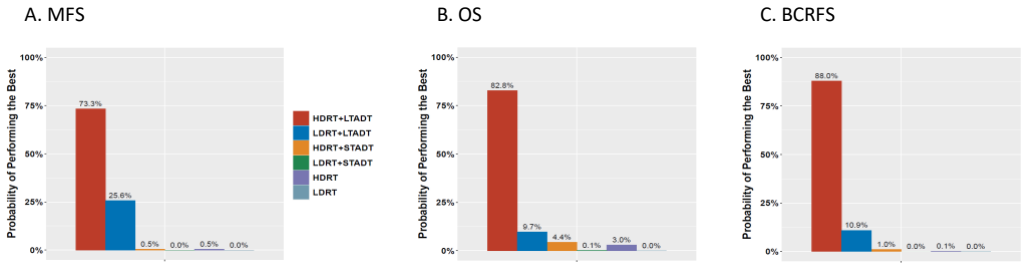
C. Biochemical Recurrence-Free Survival



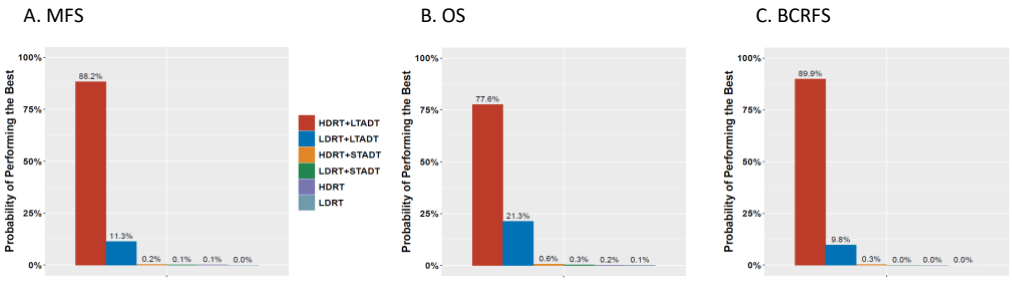
eFigure 5. Associations between Treatment Strategy and Outcomes for Patients with National Comprehensive Cancer Network (NCCN) Intermediate-Risk Disease. Note that the reference value (HR 1.00) for each forest plot is low dose radiation therapy (LDRT) alone. The hazard ratios (HRs) and 95%confidence intervals (95%CI) are presented with the associated P-score (a frequentist analog to the surface under the cumulative ranking curve) presented at the far right. HDRT, high dose radiotherapy; LTADT, long term androgen deprivation therapy; STADT, short term androgen deprivation therapy.



eFigure 6. Predicted Treatment Rankings for Metastasis-Free Survival, Overall Survival, and Biochemical Recurrence-Free Survival in Patients with National Comprehensive Cancer Network (NCCN) High-Risk Disease. Rankograms depict the six treatment strategies in terms of the surface under the cumulative ranking (SUCRA) score of which treatment is likely to be the most optimal as a percentage chance. BCRFS, biochemical recurrence-free survival; MFS, metastasis-free survival; HDRT, high dose radiotherapy; LTADT, long term androgen deprivation therapy; OS, overall survival; STADT, short term androgen deprivation therapy.

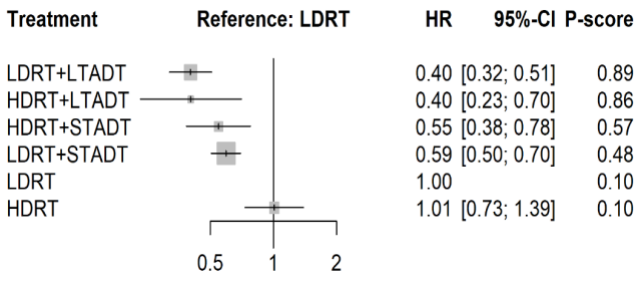


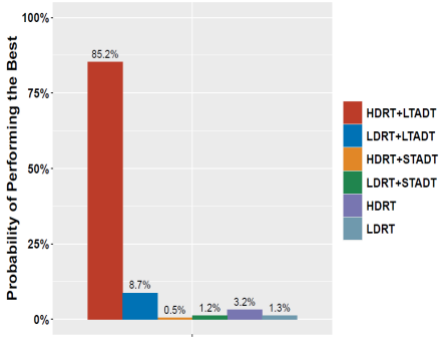
eFigure 7. Predicted Treatment Rankings for Metastasis-Free Survival, Overall Survival, and Biochemical Recurrence-Free Survival in Patients with National Comprehensive Cancer Network (NCCN) Intermediate-Risk Disease. Rankograms depict the six treatment strategies in terms of the surface under the cumulative ranking (SUCRA) score of which treatment is likely to be the most optimal as a percentage chance. BCRFS, biochemical recurrence-free survival; MFS, metastasis-free survival; HDRT, high dose radiotherapy; LTADT, long term androgen deprivation therapy; OS, overall survival; STADT, short term androgen deprivation therapy.



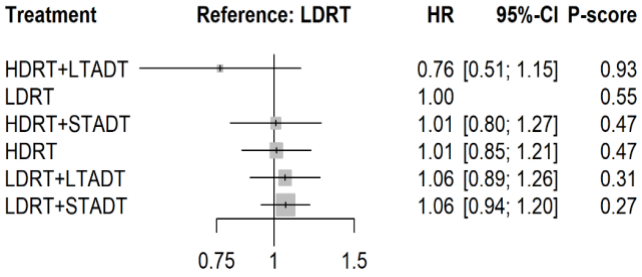
eFigure 8. Frequentist and Bayesian Network Meta-Analysis Results for Prostate Cancer-Specific and Other-Cause Mortality. Forest plots and rankograms of the six different treatment strategies with respect to prostate cancer-specific mortality (A) and other-cause mortality (B). For both forest plots, the reference value (HR 1.00) is low dose radiation therapy (LDRT) alone. The hazard ratios (HRs) and 95%confidence intervals (95%CI) are presented in ascending order, with their associated P-score (a frequentist analog to the surface under the cumulative ranking curve) presented at the far right. Rankograms depict the six treatment strategies in terms of the surface under the cumulative ranking (SUCRA) score of which treatment is likely to be the most optimal as a percentage chance. HDRT, high dose radiotherapy; LTADT, long term androgen deprivation therapy; STADT, short term androgen deprivation therapy.

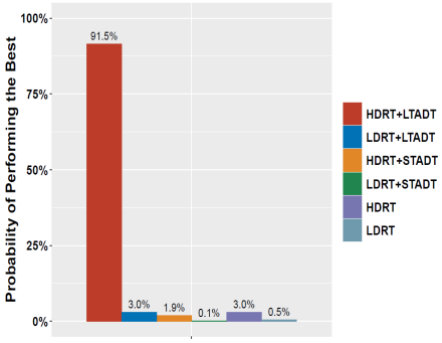
A. Prostate Cancer-Specific Mortality





B. Other-Cause Mortality





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