European Urology *Meta-Analysis*

High **D**os**E** Radiotherapy or Androgen Deprivation **T**herapy (**HEAT**) as Treatment Intensification for Localized Prostate Cancer: An Individual Patient Data Network Meta-Analysis from the MARCAP Consortium

Amar U. Kishan[†], Xiaoyan Wang, Yilun Sun, Tahmineh Romero, Jeff M. Michalski, Ting Martin Ma, Felix Y. Feng, Howard M. Sandler, Michel Bolla, Philippe Maingon, Theo De Reijke, Anouk Neven, Allison Steigler, James W. Denham, David Joseph, Abdenour Nabid, Nathalie Carrier, Luis Souhami, Matt R. Sydes, David P. Dearnaley, Isabel Syndikus, Alison C. Tree, Emma Hall, Luca Incrocci, Wilma D. Heemsbergen, Floris J. Pos, Almudena Zapatero, Jason A. Efstathiou, Araceli Guerrero, Ana Alvarez, Carmen Gonzalez San-Segundo, Xavier Maldonado, Michael Xiang, Matthew B. Rettig, Robert E. Reiter, Nicholas G. Zaorsky, Wee Loon Ong, Robert T. Dess, Michael L. Steinberg, Nicholas G. Nickols , Soumyajit Roy, Jorge A. Garcia, the MARCAP Consortium group[‡], and Daniel E. Spratt

Department of Radiation Oncology, University of California Los Angeles, Los Angeles, CA, USA (A U Kishan MD, T M Ma MD PhD, M H Xiang MD PhD, N G Nickols MD PhD, Prof M L Steinberg MD)
Department of Urology, University of California Los Angeles, Los Angeles, CA, USA (A U Kishan MD, Prof R E Reiter MD)
Division of General Internal Medicine and Health Services Research, University of California Los Angeles, Los Angeles, CA, USA (T Romero MS, X Wang PhD)
Department of Population Quantitative Health Sciences, Case Western Reserve University, Cleveland, OH, USA (Y Sun PhD, H Hartman PhD)
Department of Radiation Oncology, University Hospitals Seidman Cancer Center, Case Western Reserve University School of Medicine, Cleveland, OH, USA (Y Sun PhD, H Hartman PhD, N G Zaorsky MD, Prof D E Spratt MD)
Department of Radiation Oncology, Washington University, St. Louis, MO, USA (Prof J M Michalski MD)
Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA (Prof F Y Feng MD)
Department of Radiation Oncology, Cedars-Sinai Medical Center, Los Angeles, CA, USA (Prof H M Sandler MD)
Radiotherapy Department, University Hospital, Grenoble, France (Prof M Bolla MD)
Department of Oncology, Hematology, and Supportive Care, Sorbonne University, Paris, France (P Maingon MD)
Department of Urology, Academisch Medisch Centrum, Amsterdam, Netherland (T M de Reijke MD PhD)
Statistics Department, European Organisation for Research and Treatment of Cancer Headquarters, Brussels, Belgium (A Neven PhD**)**
Luxembourg Institute of Health, Competence Center for Methodology and Statistics, Strassen, Luxembourg (A Neven PhD)
School of Medicine and Public Health, University of Newcastle, Newcastle, NSW, Australia (A Steigler BMath, Prof J W Denham FRANZCR)
Department of Medicine and Surgery, University of Western Australia, Perth, WA, Australia (Prof D Joseph MD)
Department of Radiation Oncology, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, Quebec, Canada (A Nabid MD)
Clinical Research Center, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, Quebec, Canada (N Carrier MSc)
Department of Radiation Oncology, McGill University Health Centre, Montréal, Canada (L Souhami MD)
Medical Research Council Clinical Trials Unit at University College London, London, UK (M R Sydes PhD)
The Institute of Cancer Research, London, UK (D P Dearnaley MD, A C Tree MD, E Hall MD)
Clatterbridge Cancer Centre, Wirral, UK (I Syndikus MD)
Department of Radiation Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands (Prof L Incrocci MD)
Department of Radiation Oncology, Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands (W Heemsbergen PhD, F Pos MD)
Hospital Universitario de la Princesa, Madrid, Spain (Prof A Zapatero MD PhD)
Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA, USA (Prof J Efstathiou MD, DPhil)
Hospital Son Espases, Palma de Mallorca, Spain (A Guerrero MD)
Hospital General Universitario Gregorio Marañón, Madrid, Spain (A Alvarez MD, C G San-Segundo MD)
Hospital Universitari Vall d'Hebron, Barcelona, Spain (X Maldonado MD)
Department of Medical Oncology, University of California Los Angeles, Los Angeles, CA, USA (M B Rettig MD)
Department of Epidemiology and Preventive Medicine, Monash University, Australia (Wee Loon Ong MD)
Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, USA (R T Dess MD)
Department of Radiation Oncology, Rush University, Chicago, IL, UA (S Roy MD)
Division of Oncology, Seidman Cancer Center, Cleveland, OH, USA (J A Garcia MD)
[†]Corresponding author
[‡] Members of the consortium are listed in the Supplement (pp 16)

Corresponding Author: Amar U. Kishan, MD
Associate Professor
200 Medical Plaza
University of California, Los Angeles, Los Angeles, CA
Los Angeles, CA 90095

Abstract

Background: The relative benefits of radiotherapy (RT) dose escalation and the addition of short-term or long-term androgen deprivation therapy (STADT and LTADT) in the treatment of prostate cancer are unknown.

Objective: To perform a network meta-analysis of relevant randomized trials in order to compare the relative benefits of RT dose escalation±STADT or LTADT.

Design, settings, and participants: An individual patient data network meta-analysis of 13 multicenter randomized trials, for a total of 11,862 patients. Patients received one of the six permutations of low dose RT (64 to <74 Gy) ± STADT or LTADT or high dose RT (≥74 Gy) or high dose RT ± STADT or LTADT.**Outcome measures and statistical analyses:** Metastasis-free survival (MFS) was the primary endpoint. Frequentist and Bayesian network meta-analyses were performed to rank the various treatment strategies by MFS and biochemical recurrence-free survival (BCRFS).

Results: Median follow-up was 8.8 years (IQR 5.7-11.5). The greatest relative improvement in outcomes was seen from the addition of LTADT, irrespective of RT dose, followed by the addition of STADT, irrespective of RT dose. RT dose-escalation did not improve MFS either in the absence of ADT (HR 0.97, 95%CI 0.80-1.18) or with STADT (HR 0.99, 95%CI 0.8-1.23), or LTADT (HR 0.94, 95%CI 0.65-1.37). P-score ranking and rankogram analysis, high dose RT + LTADT was the optimal treatment strategy for both BCRFS and longer-term outcomes.

Conclusions: Conventionally escalated RT up to 79.2 Gy, alone or in the presence of ADT, does not improve MFS, while the addition of STADT or LTADT to RT alone, regardless of RT dose, consistently improves MFS. RT dose escalation does provide a high probability of improving BCRFS and, provided it can be delivered without compromising quality of life, may represent the optimal treatment strategy when used in conjunction with ADT.

Patient Summary: Radiotherapy dose escalation does not reduce the chance of developing metastases or passing away, but it does reduce the chance of having a rise in the PSA signifying a recurrence of cancer. Androgen deprivation therapy improves all outcomes. Safe dose-escalation in conjunction with androgen deprivation therapy may be the optimal treatment.

Take Home Message

We provide the strongest evidence to date for the combined benefit of radiotherapy dose escalation and ADT use/adjuvant ADT prolongation optimizes biochemical control-based outcomes. However, RT dose escalation is unlikely to improve MFS, though ADT use and adjuvant ADT prolongation consistently will.

Introduction

Radiotherapy (RT) is a standard of care treatment for localized prostate cancer.[1, 2] Non-dose-escalated external beam RT (now considered low dose RT) was first described nearly sixty years ago.[3] Several treatment intensification strategies have been studied, including RT dose-escalation and the addition of short- and long-term androgen deprivation therapy (STADT and LTADT, respectively). While these treatment strategies have consistently improved biochemical recurrence-free survival (BCRFS), improvements in distant metastasis-free survival (MFS) have varied.[4-15] This is an important distinction, as only MFS has been shown to be a surrogate endpoint for overall survival (OS).[16, 17]

Overall, six treatment strategies can be defined: low dose RT alone, low dose RT with STADT, low dose RT with LTADT, high dose RT alone, high dose RT with STADT, and high dose RT with LTADT. Due to the parallel investigation of these strategies, nearly all trials have compared only two of these with each other in the context of randomization. However, because these strategies are not without toxicity[18] so it is important to determine whether the intensification strategies have meaningful synergistic or complementary effects. Herein, we report the results of the "**H**igh Dos**E** Radiotherapy or **A**ndrogen Deprivation **T**herapy" (**HEAT**) meta-analysis, an individual patient data network meta-analysis (NMA) of 13 randomized trials. We pursued both a frequentist and a Bayesian approach to maximize the robustness of conclusions that could be drawn from the network. This project was run through the Meta-Analysis of Randomized trials in Cancer of the Prostate (MARCAP) Consortium, an international collaborative effort to form a data repository for trials investigating the treatment of prostate cancer.[19]

Methods

Search Strategy and Selection Criteria

This is an individual patient data meta-analysis. The inclusion criteria and analytical plan were pre-specified in a protocol submitted to PROSPERO (CRD42021236855). To identify all relevant randomized trials for individual patient data request, a literature review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (**Figure 1**).[20] A systematic literature search was performed using MEDLINE (1966-2020), Embase (1982-2020), trial registries (Cochrane Central Register of Controlled Trials and ClinicalTrials.gov), the Web of Science, Scopus, and major urology and oncology conference proceedings (1990-2020) to retrieve studies that evaluated RT dose escalation or the use and/or prolongation of ADT in men with localized prostate cancer receiving definitive RT. Controlled vocabulary was leveraged for studies involving humans using the following terms: randomized AND prostate AND (androgen deprivation OR hormone therapy) AND (radiotherapy OR radiation) NOT prostatectomy. The search was conducted on December 30, 2020. We had four pre-specified exclusion criteria and thus excluded trials that: (a) did not collect distant metastasis or survival data, (b) only used non-steroidal androgen receptor blockers therapy without ADT, (c) were single-center in nature, or (d) used lifelong ADT (n=10 trials excluded in total). The rationale for these criteria has been described previously.[19] The search

was conducted by a single investigator (AUK) and verified by another (DES). Our search identified 16 trials eligible for analysis. Out of these 16 trials, 13 had individual patient data available through the MARCAP consortium and were included in this network meta-analysis (**Table 1 and eTable1**).[6, 8-15, 21-23] The MARCAP consortium has been described in detail previously.[19] Briefly, it contains individual patient data from randomized clinical trials run through multiple collaborative groups including the European Organisation for Research and Treatment of Cancer (EORTC), Radiation Therapy Oncology Group (now NRG Oncology; NRG/RTOG), Medical Research Council (MRC), Institute of Cancer Research (ICR), Dutch Cancer Society (CKVO), Trans Tasman Radiation Oncology Group (TROG), Prostate Cancer Study group (PCS), and Grupo de Investigación Clínica en Oncología Radioterápica (GICOR).

Data Analysis

Low dose RT was defined as an equivalent dose in 2 Gy/fraction (assuming an α/β ratio of 3) of <74 Gy; doses ≥74 Gy were classified as high dose RT. 74 Gy was chosen as the threshold dose as it was the high dose arm on the MRC RT01 dose-escalation trial,[5] the standard arm of the CHHiP randomized trial that demonstrated the oncologic non-inferiority of a globally-used moderate hypofractionation regimen,[24] and the highest external beam dose offered on the TROG RADAR trial.[15] Patients who received a brachytherapy boost were classified as high dose RT. STADT was defined as ADT of 3-6 months duration and LTADT was defined as ADT of 18-36 months duration. ADT consisted of gonadotropin-releasing hormone agonist with or without first generation nonsteroidal androgen receptor blockers.

Six treatment strategies were defined: low dose RT, low dose RT + STADT, low dose RT + LTADT, high dose RT, high dose RT + STADT, and high dose RT + LTADT. All trials that included arms that could be classified as one of these six treatment strategies were included.

Outcomes

The primary endpoint for this study was MFS, defined as time from randomization to development of metastasis (typically detected by conventional commuted tomography or technetium bone scan imaging) or death of any cause. MFS was chosen as the primary endpoint as it is a known surrogate endpoint for OS in localized prostate cancer.[16, 25] Pre-specified secondary endpoints included OS, BCRFS, prostate cancer-specific mortality (PCSM), and other-cause mortality (OCM). All endpoints were annotated by the respective trials, most commonly as time from randomization until each respective event(s). The definition of biochemical recurrence for the purpose of BCRFS was defined by the Phoenix definition for all trials except: EORTC 22863 and EORTC 22961, in which it was defined as a PSA>1.5 ng/mL with at least two consecutive rises; RTOG 8610, in which it was defined as PSA>1.0 ng/mL at any point ≥1 year after randomization; and MRC RT01, in which it was defined as an increase in PSA to 50% above nadir and above 2 ng/mL. Distant metastasis (DM) in all trials was defined by extrapelvic disease by clinical or radiographic examination. PCSM was classified as death due to prostate cancer in all trials.

Statistical Analysis

An *a priori* statistical plan was created prior to data pooling and analysis. All analyses were performed on an intention-to-treat basis. Median follow-up time as well as the interquartile range (IQR) were calculated using the reverse Kaplan-Meier method.[25] Baseline characteristics were compared by treatment group using the Mann-Whitney U test for age and the χ^2 test for all other baseline characteristics. Between-trial heterogeneity was assessed and quantified by the basis of τ^2 and I^2**.** Publication bias was examined using Egger's test and evaluated graphically using funnel plots. These analyses were performed in R (Version 4.1.1).

For MFS, OS, and BCRFS, patient-level data were used to obtain trial-specific hazard ratio (HR) estimates of pairwise treatment effects. A frequentist network meta-analysis (NMA) approach was adopted for direct/indirect pairwise meta-analysis of treatments.[26, 27] As true effect sizes might differ from study to study, random-effects models were adopted. We first performed a frequentist NMA. In this approach, we evaluated the heterogeneity via the overall statistic I^2, as well as the Q statistics for within-design heterogeneity and inconsistency between designs. Treatments were ranked by *P* score, which measures the certainty that one treatment is better than another treatment, averaged over all competing treatments. P-scores are based solely on the point estimates and standard errors of the frequentist NMA estimates under normality assumptions and can be calculated as means of one-sided p-values. We also estimated 8-year absolute risk difference (ARD) and restricted mean survival time difference (RMSTD) for OS, MFS, and BCRFS. ARD was estimated from the Cox proportional hazards model and RMSTD was obtained from the Kaplan-Meier estimates of the survival function.

Due to variable sample sizes and event rates in each network comparison, a pre-specified Bayesian NMA was also performed. For the Bayesian NMA, a 2-stage approach was used. In stage 1, a standard regression analysis was performed to obtain aggregated data. In stage 2, a Bayesian approach was used to synthesize the results and compare the six treatment strategies with one another.[28] We used a random-effects model to account for the heterogeneity across the studies, and used Markov Chain Monte Carlo simulation to draw from the posterior distribution of the parameters. For each iteration, the ranking of all six treatment strategies was determined using the HRs from that iteration. Surface under the cumulative ranking curve (SUCRA) was calculated from these rankings[29] by summing the cumulative probabilities of all the ranks divided by the number of ranks minus 1. This statistic has no known distribution and is a means of summarizing treatment rankings. If a treatment always ranks 1, with a value of 1 denoting the most preferred treatment, then the SUCRA = 1. If a treatment always ranks last, then the SUCRA = 0, with a value of 0 denoting the least preferred treatment. The rank probabilities were also determined.

All analyses were completed with SAS version 9.4 and R version 4.0.3 (2020-10-10) at a two-tailed level of significance level of 0.05.

Results

Individual patient data were available for a total of 11,862 patients across 13 trials. Details of the included trials are shown **Table 1**, with patient characteristics shown in **Table 2.** Additional details, including heterogeneity assessments, are provided in the **eTables 1-3** and **eFigure 1**. The median follow-up was 8.8 years (interquartile range [IQR], 5.7-11.5), the median age was 70 years (IQR, 65-74), and 9%, 45%, and 45% had NCCN low-, intermediate-, and

high-risk disease, respectively. A network plot for the NMA is shown in the **eFigure 2**. A breakdown of eligible patients by treatment strategy and crude incidence for the outcomes MFS, OS, and BCRFS are shown in the **eTables 4-5**.

A forest plot for the frequentist NMA comparing MFS outcomes for the six treatment strategies, with low dose RT as the reference group, is shown in **Figure 2A**. The greatest relative improvement in outcomes was seen from the addition of LTADT, irrespective of RT dose, followed by the addition of STADT, irrespective of RT dose, but RT dose-escalation alone had no significant impact on MFS compared to low dose RT. Similar results were observed for OS (**Figure 2B**) and BCRFS (**Figure 2C**), with the exception that the numerical treatment effect estimate was improved from RT dose-escalation, particularly with respect to BCRFS, for which dose-escalation provided a clear significant benefit. Estimated 8-year ARD and RMSTD estimates for MFS, OS, and BCRFS are shown in the **eFigure 3.** Note that for the MFS endpoint, low dose RT+LTADT has a minimally higher P-score ranking than high dose RT+LTADT for both 8-year ARD and RMSTD; however, the estimates differ by -0.83% and 0.29 months, respectively. All other rankings are consistent with the HR rankings.

By P-score ordering for OS, high dose RT+LTADT emerged as the best, with low dose RT+LTADT as a close-second. Analyses stratified by NCCN intermediate vs. NCCN high risk are shown in the **eFigures 4-5**. The results are consistent with the overall analysis, though for NCCN high-risk disease, low-dose RT+LTADT had a higher P-score for the endpoints of MFS and OS, with considerably wider confidence intervals for the estimates for high-dose RT+LTADT in this subset when compared with the overall population.

The results of pre-specified comparisons pertaining to addition or prolongation of ADT to low or high dose RT or escalating dose in the absence of presence of ADT, are shown in **Table 3**. RT dose-escalation did not significantly improve MFS compared to low dose RT in the absence of ADT (HR 0.97, 95%CI 0.80-1.18, p=0.7), in the presence of STADT (HR 0.99, 95%CI 0.8-1.23, p=0.97), or in the presence of LTADT (HR 0.94, 95%CI 0.65-1.37, p=0.98). Adding STADT or LTADT, or prolonging STADT to LTADT, significantly improved MFS in the presence of low and high dose RT, with the exception of the addition of STADT to high dose RT, which did not significantly improve MFS in a pairwise comparison (HR 0.85, 95%CI 0.68-1.06).

Due to variable sample sizes and event rates in each network comparison, a Bayesian approach was employed. Summary rankograms generated using the posterior probability for each treatment being the best, as well as SUCRA scores, are shown in **Figure 3** for the endpoints MFS, OS, and BCRFS. For MFS, high dose RT + LTADT had a 50.0% chance of being ranked the optimal treatment, with low dose RT + LTADT as a close second option at 49.0%. For OS, high dose RT + LTADT had an 81.2% chance of being ranked the optimal treatment, with low dose RT + LTADT as a distant second (17.2%). For BCRFS, high dose RT + LTADT had a 68.1% chance of being ranked the optimal treatment, with low dose RT + LTADT again being a distant second (30.7%). For all endpoints, the other four strategies had a $\leq$1.0% chance of being ranked as optimal. Analyses stratified by NCCN intermediate vs. NCCN high risk are shown in

eFigures 6-7. The findings from these subgroup analyses are consistent with the primary findings.

Because the rankograms indicated a markedly higher chance of high dose RT + LTADT being optimal with respect to OS versus MFS (81.5% vs. 49.7%), we repeated both the frequentist and the Bayesian NMAs for the endpoints of PCSM and OCM. Forest plots and rankograms are shown in the **eFigure 8**. By frequentist ranking, low dose RT + LTADT narrowly surpasses high dose RT + LTADT for PCSM (P scores of 0.89 vs. 0.86), while for OCM, high dose RT + LTADT far outranks low dose RT + LTADT (P scores of 0.93 vs. 0.31). By rankogram analysis, high dose RT + LTADT emerged as the highest ranked strategy for both PCSM (85.2%) and OCM (91.5%).

Discussion

These data represent, to our knowledge, the first NMA from individual patient data across treatment strategies in localized prostate cancer. Although in an ideal world every treatment strategy would have direct randomized comparisons, this would require 64 randomized trials to assess every single treatment strategy in our NMA. Our results demonstrate that RT dose-escalation does not significantly improve MFS, irrespective of ADT use or ADT duration, with a low probability that it would result in superior MFS outcomes. In contrast, with high probability, STADT and LTADT improve MFS irrespective of RT dose. Importantly, RT dose-escalation had a modest to high probability of improving BCRFS irrespective of STADT or LTADT. Based on the P-score rankings in the frequentist NMA and the rankograms from the Bayesian NMA high dose RT + LTADT appears to be the optimal treatment strategy for all endpoints. These findings are of significant clinical relevance and questions strategies that escalate RT dose in lieu of adding (or prolonging) ADT.

The present results strengthen previously underpowered observations about the importance of ADT even in the context of dose-escalated RT. The results also demonstrates that further RT dose intensification, even in the context of LTADT has a high probability of improving BCRFS. Further, high dose RT+LTADT consistently emerges as the optimal treatment with regards to MFS and OS as well. However, the margin of benefit over low dose RT+LTADT remains unclear, since by direct pairwise comparison, the differences are not statistically significant. Prior retrospective non-randomized data has suggested that RT dose-escalation can improve MFS in certain situations, however randomized trials to date have been unable to replicate these findings in intermediate risk disease without ADT[7] or intermediate/high risk disease with an intermediate ADT duration[30]. Moreover, our exploratory analysis of PCSM and OCM highlights that improvements in OCM (which might be attributable to factors we cannot account for, such as improved general medical care over time) might significantly be influencing P-score and rankogram results with respects to OS. Nonetheless, the overall results support the concept that dose-escalation, if delivered safely, optimizes BCRFS even in the presence of LTADT.

There are limitations to this analysis. NMAs rely on homogeneity between trials of similar interventions, transitivity between trials of different interventions, and consistency

between direct and indirect evidence.[31] Given that the NMA included 11,862 patients enrolled across 13 trials that spanned from 1987-2010, there are inherent limitations to this methodology. We did not find any evidence of publication bias, but there was heterogeneity in the MFS and BCRFS endpoints. We used two separate NMA approaches to increase the robustness of our approach, and found remarkably consistent findings. Notably, the rankogram analysis is sensitive to small differences in effect size, which may in part explain why the rankogram analysis more readily ranked high dose RT + LTADT as an optimal strategy than the P-score ranking did. Gleason grade migration over time and lack of on biopsy core positivity data precludes more granular stratification of intermediate risk disease. Thus, the generalizability to contemporary favorable intermediate risk disease and unfavorable intermediate risk disease is unclear. Emerging data suggest that underlying transcriptomic heterogeneity may drive outcomes, and such data were not available for incorporation in this analysis. Future trials, such NRG GU009 and GU010 will test these hypotheses.[32, 33] Dose-escalation was performed via conventional fractionation, with 237 patients receiving a brachytherapy boost. Microboosts and SBRT were not used in any of the included trials. However, there are no prospective data to support a MFS benefit to using these RT delivery methods,[34, 35] and data from the TROG RADAR trial indicate a similar relationship between ADT prolongation and RT with or without a brachytherapy boost.[36, 37] Thus, it is unclear if inclusion of other forms of RT dose-escalation would impact our results. Finally, novel imaging techniques such as PSMA-PET are likely to identify subsets of patients with non-localized disease both at presentation and at relapse.[38, 39] These would impact both patient selection and also endpoint detection. Currently, the prognostic impact of upstaging by such advanced imaging remains unknown.[40] Finally, we do not have information on toxicity, either physician-scored or patient-reported, and a toxicity evaluation will be the subject of another study.

Conclusions

In conclusion, these results demonstrate that the relative benefit of adding or prolonging ADT when treating localized prostate cancer with RT exceeds the benefit of escalating RT dose up to 79.2 Gy or its equivalent. Specifically, demonstrate the relative benefit of adding or prolonging ADT when treating prostate cancer with RT, despite a well-recognized impact of ADT on the quality of life of patients and of its financial toxicity. However, RT dose-escalation improves BCRFS regardless of ADT strategy deployed and may have clinical advantages if delivered without worsening of quality of life. High dose RT+LTADT appears to be the treatment strategy that is most likely to prolong MFS with respect to low dose RT. Biomarker discovery and validation efforts will be integral to choosing the optimal treatment intensification strategy for any given patient.

Figure Legends

Figure 1. PRISMA diagram. Details on included trials, as well as excluded trials (and reason for exclusion) are provided in Table 1 and Appendix A2-4. ADT, androgen deprivation therapy; DM, distant metastasis; IPD, individual patient data; OS, overall survival.

Figure 2. Forest Plot Derived from Frequentist Network Meta-Analysis of Treatment Strategy Impact on Survival Outcomes. 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.

Figure 3. Predicted Treatment Rankings for Metastasis-Free Survival, Overall Survival, and Biochemical Recurrence-Free Survival. 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; HDRT, high dose radiotherapy; LTADT, long term androgen deprivation therapy; MFS, metasasis-free survival; OS, overall survival; STADT, short term androgen deprivation therapy.

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