Treatments for Metastatic Hormone-sensitive Prostate Cancer: Systematic Review, Network Meta-analysis, and Benefit-harm assessment.

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Multiple treatments for metastatic, hormone-sensitive prostate cancer (mHSPC) are available, but their effects on health-related quality of life (HRQoL) and benefit-harm balance remain unclear.; To assess clinical effectiveness regarding survival and HRQoL, safety, and benefit-harm balance of mHSPC treatments.; We searched MEDLINE, EMBASE, CENTRAL, and ClinicalTrials.gov until March 1, 2022. Randomized controlled trials (RCTs) comparing docetaxel, abiraterone, enzalutamide, apalutamide, darolutamide, and radiotherapy combined with androgen deprivation therapy (ADT) mutually or with ADT alone were eligible. Three reviewers independently performed screening, data extraction, and risk of bias assessment in duplicate.; Across ten RCTs, we found relevant survival benefits for ADTă+ădocetaxel (high certainty according to the Grading of Recommendations, Assessment, Development and Evaluation [GRADE]), ADTă+ăabiraterone (moderate certainty), ADTă+ăenzalutamide (low certainty), ADTă+ăapalutamide (high certainty), and ADTă+ădocetaxelă+ădarolutamide (high certainty) compared with ADT alone. ADTă+ăradiotherapy appeared effective only in low-volume de novo mHSPC. We found a short-term HRQoL decrease lasting 3-6 mo for ADTă+ădocetaxel (moderate certainty) and a potential HRQoL benefit for ADTă+ăabiraterone up to 24 mo of follow-up (moderate certainty) compared with ADT alone. There was no difference in HRQoL for ADTă+ăenzalutamide, ADTă+ăapalutamide, or ADTă+ăradiotherapy over ADT alone (low-high certainty). Grade 3-5 adverse effect rates were increased with all systemic combination treatments. A benefit-harm assessment showed high probabilities (>60%) for a net clinical benefit with ADTă+ăabiraterone, ADTă+ăenzalutamide, and ADTă+ăapalutamide, while ADTă+ădocetaxel and ADTă+ădocetaxelă+ădarolutamide appeared unlikely (<40%) to be beneficial.; Despite substantial survival benefits, no systemic combination treatment showed a clear HRQoL improvement compared with ADT alone. We found evidence for a short-term HRQoL decline with ADTă+ădocetaxel and a higher net clinical benefit with ADTă+ăabiraterone, ADTă+ăapalutamide and ADTă+ăenzalutamide. While individualized decision-making remains important and economic factors need to be considered, the evidence may support a general preference for the combination of ADT with androgen receptor axis-targeted therapies over docetaxel-containing strategies.; We assessed different combination treatments for metastatic hormone-sensitive prostate cancer. While survival was better with all systemic combina-

tion treatments, there was no clear improvement in health-related quality of life compared with androgen deprivation therapy alone. Novel hormonal combination treatments had a more favorable benefit-harm balance than combination treatments that include chemotherapy.

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