Treatment Modality	Advantages	Disadvantages	Evidence	
Radiotherapy			Studies	Outcomes
Dose Escalation				
Brachytherapy Boost	Long-term durable improvement in biochemical control vs. EBRT boost No change in GU morbidity with HDR boost	No overall survival benefit vs. EBRT boost Increased acute and late GU morbidity with LDR boost Trend towards increased GI morbidity	ASCENDE-RT: dose-escalation with LDR brachytherapy boost vs. EBRT boost	15-year biochemical progression-free survival 80% with brachytherapy boost vs. 53% with EBRT boost GU morbidity higher in LDR brachytherapy arm
Focal Lesion Boost	Improved biochemical control vs. no boost No increased GI or GU toxicity	No benefit to prostate cancer-specific survival or overall survival apparent too date Dominant intraprostatic lesion delineation requires expertise	FLAME: mpMRI-guided focal boost to macroscopically visible tumor vs. no boost	5-year biochemical disease-free survival improved with focal boost (HR: 0.45)
SBRT	Patient convenience Resource allocation	Mild increased GU toxicity	HYPO-PROST: 15Gy/2 boost vs. Conventional fractionation after 46Gy to pelvis HYPO-RT-PC: ultra-hypofractionation vs. conventional fractionation	No difference in 5-year biochemical-free survival, metastasis-free survival or overall survival No difference in 5-year failure-free survival Grade 2 or worse GU toxicity 6% vs. 2%
Elective Nodal irradiation	Two studies that demonstrate improved biochemical control	Longer follow-up is required True value yet to be clarified but awaiting RTOG 0924	RTOG 0534: prostate bed RT alone vs. addition of ADT vs. ADT + elective nodal EBRT	5-year biochemical progression-free survival 71%, 83% and 89%, respectively

			POP-RT: whole pelvis EBRT vs. prostate only EBRT in high-risk N0 patients	Whole pelvis EBRT improved 5-year biochemical progression-free survival (HR: 0.23), 5-year disease-free survival (HR: 0.40) and 5-year metastasis-free survival (HR: 0.35), but did not impact overall survival
Systemic Therapy				
ADT				
Adjuvant (concurrent and following RT)	Improved time until progression and reduced incidence of metastases vs. neoadjuvant		Meta-analysis of OTT-0101 and RTOG 9413: adjuvant vs. neoadjuvant ADT	Reduced risk of metastasis with adjuvant ADT (HR: 1.40) and absolute difference of 10.8 months in mean survival time for progression
Docetaxel	Improved 4-year overall survival when combined with RT + ADT (in RTOG 0521) Improved relapse-free survival (in GETUG-12) Improved failure-free survival (in STAMPEDE)	Adverse events doubled with addition of docetaxel (in RTOG 0521) No difference in metastasis-free survival or cancer-specific survival (in GETUG-12) No benefit to overall survival (in STAMPEDE)	RTOG 0521: RT + ADT + docetaxel vs. RT + ADT GETUG-12: ADT + docetaxel + extramustine vs. ADT	4-year overall survival 93% vs. 89% Significantly improved 12-year relapse-free survival (HR 0.75), but no difference in metastasis-free survival or cancer-specific survival

			STAMPEDE: standard of care + docetaxel vs. standard of care	Improved failure-free survival (HR 0.70), but no overall survival benefit
Abiraterone	Improved failure-free survival and overall survival vs. ADT		STAMPEDE: ADT vs. ADT + abiraterone + prednisone	Improved failure-free survival (HR: 0.21) and overall survival (HR: 0.61)
Immunotherapy	Evidence of benefit in metastatic castrate-resistant setting	No level 1 evidence of benefit in high-risk setting	KEYNOTE-1999: metastatic castrate-resistant prostate cancer treated with pembrolizumab	Disease control varied with PD-L1 expression and varied between 9% and 22%
PARP inhibitors	Identifying more genes that are important in biological aggressiveness of prostate cancer that can potentially be targeted Mounting evidence of utility in metastatic castrate-resistant setting	No level 1 evidence of benefit in high-risk setting	PROfound: metastatic castrate-resistant prostate cancer with alteration in BRCA1, BRCA2 or ATM or alterations in 12 other DNA damage repair genes treated with olaparib or enzalutamide/abiraterone	Improved progression-free survival (HR: 0.34) with median overall survival of 18.5 months in cohort A and 15.1 months in cohort B
Surgery	Some retrospective reviews suggest similar outcomes with RT Greater use of MRI and PET may select patients appropriate for surgery	No randomized data comparing surgery and RT in high-risk patients	No prospective data	

Table S1. The advantages and disadvantages of various treatment options in the management of patients with high-risk prostate cancer.