Locally Advanced, High-Risk Prostate Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. Moyer VA. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2012;157(2):120-134.	Review/Other-Tx	N/A	U.S. Preventive Services Task Force (USPSTF) reviewed new evidence on the benefits and harms of PSA–based screening for prostate cancer, as well as the benefits and harms of treatment of localized prostate cancer.	The USPSTF recommends against PSA-based screening for prostate cancer (grade D recommendation). This recommendation applies to men in the general U.S. population, regardless of age. This recommendation does not include the use of the PSA test for surveillance after diagnosis or treatment of prostate cancer; the use of the PSA test for this indication is outside the scope of the USPSTF.	4
2. Whitmore WF, Jr. Natural history of low-stage prostatic cancer and the impact of early detection. *Urol Clin North Am.* 1990;17(4):689-697.	Review/Other-Dx	N/A	An expanding and increasingly older population, a rising incidence of prostate cancer, and uncertainties regarding treatment effectiveness has made this disease a target of special concern. The natural history of the cancer must be a consequence of host-tumor interactions, but little is known for sure about this subject. The growth rate of the tumor is determined by many factors, including genetic instability. At present, tumor grade, volume, and ploidy are the most useful techniques for judging the growth rate and metastatic potential. Stage A1 tumors generally are indolent, whereas stage A2 tumors are more aggressive. The natural history of stage B lesions is not well documented. The author asks 2 questions (Is cure necessary in those in whom it may be possible? Is cure possible in those in whom it may be necessary?); and reviews the problems inherent in screening for prostate cancer at this time.	No results reported in abstract.	4
3. Ciezki JP, Hsu IC, Abdel-Wahab M, et al. American College of Radiology Appropriateness Criteria((R))--locally advanced (high-risk) prostate cancer. *Clin Oncol (R Coll Radiol).* 2012;24(1):43-51.	Review/Other-Tx	N/A	Evidence-based guidelines to assist referring physicians and other providers in making the most appropriate imaging or treatment decision for a specific clinical condition.	N/A	4

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4. Bolla M, van Poppel H, Tombal B, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). *Lancet.* 2012;380(9858):2018-2027.	Experimental-Tx	1,005 patients	To report the long-term results of a trial of immediate postoperative irradiation vs a wait-and-see policy in patients with prostate cancer extending beyond the prostate, to confirm whether previously reported progression-free-survival was sustained.	1,005 patients were randomly assigned to a wait-and-see policy (n=503) or postoperative irradiation (n=502) and were followed up for a median of 10.6 years (range 2 months to 16.6 years). Postoperative irradiation significantly improved bPFS compared with the wait-and-see policy (198 [39.4%] of 502 patients in postoperative irradiation group vs 311 [61.8%] of 503 patients in wait-and-see group had biochemical or clinical progression or died; HR 0.49 [95% CI, 0.41–0.59]; $P<0.0001$). Late adverse effects (any type of any grade) were more frequent in the postoperative irradiation group than in the wait-and-see group (10 year cumulative incidence 70.8% [66.6–75.0] vs 59.7% [55.3–64.1]; $P=0.001$).	1
5. Wiegel T, Bottke D, Steiner U, et al. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. *J Clin Oncol.* 2009;27(18):2924-2930.	Experimental-Tx	388 patients (114 had RT and 154 "wait and see")	Randomized phase III results of ART vs "wait and see" in patients with pT3 prostate cancer following RP.	Biochemical control at 5 years increased to 72% for RT arm compared with 54% for wait and see ($P=.0015$, HR 0.53). The rate of late grade 3-4 side effects was 0.3%. ART for pT3 prostate cancer significantly reduces the risk of biochemical progression after RP. The rate of side effects is very low.	1
6. Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. *J Urol.* 2009;181(3):956-962.	Experimental-Tx	425 patients	Long-term follow-up of a randomized clinical trial of RT to reduce the risk of subsequent metastatic disease and death. 211 men were randomized to observation and 214 to ART.	Metastasis-free survival was significantly greater with RT (93/214 events on the RT arm vs 114/211 events on observation). Survival improved significantly with ART (88 deaths of 214 on the RT arm vs 110 deaths of 211 on observation). ART after RP for a man with pT3N0M0 prostate cancer significantly reduces the risk of metastasis and increases survival.	1

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7. Barrett T, Gill AB, Kataoka MY, et al. DCE and DW MRI in monitoring response to androgen deprivation therapy in patients with prostate cancer: a feasibility study. *Magn Reson Med.* 2012;67(3):778-785.	Observational-Dx	23 consecutive patients	To evaluate 3.0T dynamic contrast-enhanced MRI and diffusion-weighted MRI in monitoring ADT response.	23 consecutive patients with prostate cancer treated by primary ADT were included. Imaging was performed at baseline and 3 months post-treatment with ADT. After 3 months therapy there was a significant reduction in all dynamic contrast-enhanced MRI parameters measured in tumor regions of interest (K(trans), k(ep), v(p), IAUGC-90); $P<0.001$. Areas of normal-appearing peripheral zone showed no significant change; $P=0.285–0.879$. Post-ADT, there was no significant change in apparent diffusion coefficient values in tumors, whilst apparent diffusion coefficient values significantly decreased in areas of normal-appearing peripheral zone, from 1.786 x 10(-3) mm(2) /s to 1.561 x 10(-3) mm(2) /s; $P=0.007$. As expected the median PSA significantly reduced from 30 ng/mL to 1.5 ng/mL post-treatment, and median prostate volume dropped from 47.6 cm(3) to 24.9 cm(3) ; $P<0.001$.	3
8. Boorjian SA, Karnes RJ, Viterbo R, et al. Long-term survival after radical prostatectomy versus external-beam radiotherapy for patients with high-risk prostate cancer. *Cancer.* 2011;117(13):2883-2891.	Observational-Tx	1,238 patients underwent RP, and 609 patients received with EBRT	To compare the outcomes after RP and EBRT for patients who were classified with high-risk prostate cancer according to NCCN criteria.	The 10-year cancer-specific survival rate was 92%, 92%, and 88% after RRP, EBRT plus ADT, and EBRT alone, respectively ($P=.06$). After adjustment for case mix, no significant differences in the risks of systemic progression (HR, 0.78; 95% CI, 0.51–1.18; $P=.23$) or prostate cancer death (HR, 1.14; 95% CI, 0.68–1.91; $P=.61$) were observed between patients who received EBRT plus ADT and patients who underwent RP. The risk of all-cause mortality, however, was greater after EBRT plus ADT than after RP (HR, 1.60; 95% CI, 1.25–2.05; $P=.0002$).	2

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9. Warde P, Mason M, Ding K, et al. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. *Lancet.* 2011;378(9809):2104-2111.	Experimental-Tx	1,205 patients assigned (602 in the ADT only group and 603 in the ADT and RT group)	To assess the role of local RT in addition to ADT in patients with locally advanced prostate cancer.	Median follow-up was 6.0 years (IQR 4.4–8.0). At the time of analysis, a total of 320 patients had died, 175 in the ADT only group and 145 in the ADT and RT group. The addition of RT to ADT improved OS at 7 years (74%, 95% CI, 70–78 vs 66%, 60–70; HR 0.77, 95% CI, 0.61–0.98, *P*=0·033). Both toxicity and health-related QoL results showed a small effect of RT on late gastrointestinal toxicity (rectal bleeding grade >3, 3 patients (0·5%) in the ADT only group, 2 (0·3%) in the ADT and RT group; diarrhea grade >3, 4 patients (0·7%) vs 8 (1·3%); urinary toxicity grade >3, 14 patients (2·3%) in both groups).	1
10. Widmark A, Klepp O, Solberg A, et al. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. *Lancet.* 2009;373(9660):301-308.	Experimental-Tx	875 patients randomized to endocrine treatment alone; 439 patients or to the same endocrine treatment combined with RT ;436 patients	Open phase III study comparing endocrine therapy with and without local RT, followed by castration on progression to assess the effect of RT.	After a median follow-up of 7.6 years, 79 men in the endocrine alone group and 37 men in the endocrine plus RT group had died of prostate cancer. The cumulative incidence at 10 years for PCSM was 23.9% in the endocrine alone group and 11.9% in the endocrine plus RT group (difference 12.0%, 95% CI 4.9%–19.1%), for a relative risk of 0.44 (0.30–0.66). At 10 years, the cumulative incidence for overall mortality was 39.4% in the endocrine alone group and 29.6% in the endocrine plus RT group (difference 9.8%, 0.8%–18.8%), for a relative risk of 0.68 (0.52–0.89). Cumulative incidence at 10 years for PSA recurrence was substantially higher in men in the endocrine-alone group (74.7% vs 25.9%, *P*<0.0001; HR 0.16; 0.12–0.20). After 5 years, urinary, rectal, and sexual problems were slightly more frequent in the endocrine plus RT group.	1
11. The NCCN Clinical Practice Guidelines in Oncology™ Prostate Cancer V.1.2015 © 2015 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.	Review/Other-Tx	N/A	To provide guidelines in prostate cancer.	No abstract available.	4

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12. Pilepich MV, Winter K, Lawton CA, et al. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma--long-term results of phase III RTOG 85-31. *Int J Radiat Oncol Biol Phys.* 2005;61(5):1285-1290.	Experimental-Tx	977 patients 488 adjuvant arm (Arm I) 489 observation arm (Arm II)	Randomized phase III trial to evaluate the effectiveness of adjuvant androgen suppression, using goserelin, in unfavorable prognosis carcinoma of the prostate treated with definitive RT.	At 10 years, the absolute survival rate was significantly greater for the adjuvant arm than for the control arm: 49% vs 39%, respectively (P=0.002). The 10-year local failure rate for the adjuvant arm was 23% vs 38% for the control arm (P<0.0001). The corresponding 10-year rates for the incidence of DM and disease-specific mortality was 24% vs 39% (P<0.001) and 16% vs 22% (P=0.0052), respectively, both in favor of the adjuvant arm.	1
13. Roach M, 3rd, Bae K, Speight J, et al. Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: long-term results of RTOG 8610. *J Clin Oncol.* 2008;26(4):585-591.	Experimental-Tx	456 patients 224 ADT and EBRT; 232 EBRT alone	To summarize long-term follow-up results; update the long-term results of RTOG 8610 and confirm the important clinical benefits of adding short-term ADT to EBRT in patients with high-risk, locally advanced disease.	10-year OS estimates (43% vs 34%) and median survival times (8.7 vs 7.3 years) favored ADT and EBRT, respectively; however, these differences did not reach statistical significance (P=0.12). There was a statistically significant improvement in 10-year disease-specific mortality (23% vs 36%; P=0.01), distant metastasis (35% vs 47%; P=0.006), DFS (11% vs 3%; P<0.0001), and BF (65% v 80%; P<0.0001) with the addition of ADT, but no differences were observed in the risk of fatal cardiac events. The addition of 4 months of ADT to EBRT appears to have a dramatic impact on clinically meaningful end points in men with locally advanced disease with no statistically significant impact on the risk of fatal cardiac events.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
14. Bolla M, Van Tienhoven G, Warde P, et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. *Lancet Oncol.* 2010;11(11):1066-1073.	Experimental-Tx	415 total patients; 208 RT alone 207 combined treatment	Randomized phase III trial to assess the benefit of the addition of long-term androgen suppression with a luteinizing-hormone-releasing hormone agonist to EBRT in patients with prostate cancer with high metastatic risk.	Median follow-up was 9.1 years (IQR 5.1–12.6). 10-year clinical DFS was 22.7% (95% CI, 16.3–29.7) in the RT-alone group and 47.7% (39.0–56.0) in the combined treatment group (HR 0.42, 95% CI, 0.33–0.55, $P<0.0001$). 10-year OS was 39.8% (95% CI, 31.9–47.5) in patients receiving RT alone and 58.1% (49.2–66.0) in those allocated combined treatment (HR 0.60, 95% CI, 0.45–0.80, $P=0.0004$), and 10-year prostate-cancer mortality was 30.4% (95% CI, 23.2–37.5) and 10.3% (5.1–15.4), respectively (HR 0.38, 95% CI, 0.24–0.60, $P<0.0001$). In patients with prostate cancer with high metastatic risk, immediate androgen suppression with a luteinizing-hormone-releasing hormone agonist given during and for 3 years after EBRT improves 10-year DFS and OS without increasing late cardiovascular toxicity.	1
15. Zelefsky MJ, Eastham JA, Cronin AM, et al. Metastasis after radical prostatectomy or external beam radiotherapy for patients with clinically localized prostate cancer: a comparison of clinical cohorts adjusted for case mix. *J Clin Oncol.* 2010;28(9):1508-1513	Observational-Tx	2,380 patients	To assess the effect of RP and EBRT on DM rates in patients with localized prostate cancer treated with RP or EBRT at a single specialized cancer center.	The 8-year probability of freedom from metastatic progression was 97% for RP patients and 93% for EBRT patients. After adjustment for case mix, surgery was associated with a reduced risk of metastasis (HR, 0.35; 95% CI, 0.19–0.65; $P<0.001$). Results were similar for PCSM (HR, 0.32; 95% CI, 0.13–0.80; $P=0.015$). Rates of metastatic progression were similar for favorable-risk disease (1.9% difference in 8-year metastasis-free survival), somewhat reduced for intermediate-risk disease (3.3%), and more substantially reduced in unfavorable-risk disease (7.8% in 8-year metastatic progression).	2

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16. Taira AV, Merrick GS, Galbreath RW, et al. Long-term outcomes of prostate cancer patients with Gleason pattern 5 treated with combined brachytherapy and external beam radiotherapy. *Brachytherapy.* 2013;12(5):408-414.	Observational-Tx	329 patients	To report outcomes of men with Gleason grade 5 treated with brachytherapy to help determine the efficacy of brachytherapy in this patient population.	At 10 years, bPFS, CSS, and OS for the group of high-risk patients as a whole was 91.1%, 95.5%, and 72.5%, respectively. There was no difference in bPFS between men with and without Gleason pattern 5 (89.7% vs 91.8%; *P*=0.56). However, men with Gleason pattern 5 had lower prostate cancer CSS (90.3% vs 98.1%; *P*=0.011). There was no difference in OS comparing men with and without Gleason pattern 5 disease (67.7% vs 75.4%; *P*=0.14).	2
17. Bittner N, Merrick GS, Butler WM, et al. Long-term outcome for very high-risk prostate cancer treated primarily with a triple modality approach to include permanent interstitial brachytherapy. *Brachytherapy.* 2012;11(4):250-255.	Observational-Tx	131 patients	To evaluate outcome in the most unfavorable subset of high-risk prostate cancer patients treated with a combination of supplemental EBRT and brachytherapy.	The median pretreatment PSA and GS were 11.0ng/mL and 8. 110 (84%) patients had a GS ≥8. At 9 and 12 years, the CSS, bPFS, and OS were 91.0% and 86.5%, 87.3% and 87.3%, and 70.5% and 60.5%, respectively. The most common cause of death was heart disease (22.2%) with deaths from nonprostate cancer (12.7%) and prostate cancer (8.3%) being less likely.	2
18. Stock RG, Cesaretti JA, Hall SJ, Stone NN. Outcomes for patients with high-grade prostate cancer treated with a combination of brachytherapy, external beam radiotherapy and hormonal therapy. *BJU Int.* 2009;104(11):1631-1636.	Observational-Tx	181 patients	To assess the outcomes for patients with GS 8-10 prostate cancer treated with brachytherapy, EBRT and HT.	The 8-year actuarial FFbF, freedom from DM, prostate-cancer specific survival and OS were 73%, 80%, 87% and 79%, respectively. The pretreatment PSA level significantly affected FFbF, with 8-year rates of 72%, 82% and 58% for patients with PSA level of ≤10, >10–20 and >20 ng/mL, respectively (*P*=0.006). The PSA level had no significant effect on rates of DM. The GS had the most significant affect on FFbF in a multivariate analysis, and was the only factor to significantly affect rates of DM; the 8-year FFbF rates were 84%, 55% and 30% for scores of 8, 9 and 10, respectively (*P*=0.003). The corresponding freedom from DM and prostate-cancer specific survival rates were 86%, 76%, 30% (*P*<0.001) and 92%, 80%, 62.5% (*P*=0.003), respectively.	2

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19. Feng FY, Qian Y, Stenmark MH, et al. Perineural invasion predicts increased recurrence, metastasis, and death from prostate cancer following treatment with dose-escalated radiation therapy. *Int J Radiat Oncol Biol Phys.* 2011;81(4):e361-367.	Observational-Tx	651 men	To assess the prognostic value of PNI for patients treated with dose-escalated EBRT for prostate cancer.	PNI was present in 34% of specimens at biopsy and was significantly associated with higher GS, T stage, and PSA level. On univariate and multivariate analysis, the presence of PNI was associated with worse FFbF (HR = 1.7, P<0.006), FFM (HR = 1.8, P<0.03), and CSS (HR = 1.4, P<0.05) compared with absence of PNI; there was no difference in OS. 7-year rates of FFbF, FFM, and CSS were 64% vs 80%, 84% vs 92%, and 91% vs 95% for those patients with and without PNI, respectively. On recursive partitioning analysis, PNI predicted for worse FFM and CSS in patients with GS 8-10, with FFM of 67% vs 89% (P<0.02), and CSS of 69% vs 91%, (P<0.04) at 7 years for those with and without PNI, respectively.	2
20. Huang J, Vicini FA, Williams SG, et al. Percentage of positive biopsy cores: a better risk stratification model for prostate cancer? *Int J Radiat Oncol Biol Phys.* 2012;83(4):1141-1148	Observational-Tx	1,056 patients	To assess the prognostic value of the percentage of positive biopsy cores and PNI in predicting the clinical outcomes after RT for prostate cancer and to explore the possibilities to improve on existing risk-stratification models.	On multivariate Cox regression analysis, the positive biopsy cores was an independent predictor of distant metastasis, CSS, and OS (all P<.05). A positive biopsy cores >50% was associated with significantly greater distant metastasis (HR, 4.01; 95% CI, 1.86–8.61), and its independent predictive value remained significant with or without ADT (all P<.05). In contrast, PNI and T stage were only predictive for locoregional recurrence. Combining the positive biopsy cores (≤50% vs >50%) with National Comprehensive Cancer Network (NCCN) risk stratification demonstrated added prognostic value of distant metastasis for the intermediate-risk (HR, 5.44; 95% CI, 1.78–16.6) and high-risk (HR, 4.39; 95% CI, 1.70–11.3) groups, regardless of the use of ADT and high-dose RT (all P<.05). The proposed positive biopsy cores classification appears to provide improved stratification of the clinical outcomes relative to the NCCN classification.	2

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21. Yamoah K, Stone N, Stock R. Impact of race on biochemical disease recurrence after prostate brachytherapy. *Cancer*. 2011;117(24):5589-5600.	Observational-Tx	2,268 patients	To examine the influence of race on biochemical DFS among men who received prostate brachytherapy.	In this series, a total of 2,268 patients included 81% Caucasians, 12% African Americans, 6% Hispanics, and 1% Asians. The 10-year actuarial FFbF rate was 70% for African American men and 84% for all others (*P*=.002). Between Caucasian men and African American men, the 10-year FFbF rate was 83% vs 70%, respectively (*P*=.001).There was no significant difference in 10-year FFbF between Caucasian men and Hispanic men (83% vs 86%, respectively; *P*=.6). The 10-year FFbF rate for Hispanic men and African American men was 86% vs 70%, respectively (*P*=.062). A greater percentage of African American men presented with higher PSA levels (>10 ng/mL; 44% vs 21%; *P*<.001) and, thus, with higher risk disease (24% vs 15%; *P*<.001) compared with Caucasian men. Among the men with low-risk disease, the 10-year FFbF rate was 90% for Caucasian men and 76% for African American men (*P*=.041). The 10-year biochemical DFS rate for patients who received brachytherapy alone was 86% for Caucasian men and 61% for African American men (*P*=.001); however, this difference was not observed when brachytherapy was combined with ADT with or without supplemental EBRT. Multivariate analysis revealed that PSA (*P*=.024), GS (*P*<.001), the biologic effective dose (*P*<.001), EBRT (*P*=.002), ADT (*P*=.03), and African American race (*P*=.037) were significant predictors of 10-year FFbF. No significant differences were observed in OS, CSS, or distant metastasis-free survival between racial groups.	2

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22. Jackson W, Hamstra DA, Johnson S, et al. Gleason pattern 5 is the strongest pathologic predictor of recurrence, metastasis, and prostate cancer-specific death in patients receiving salvage radiation therapy following radical prostatectomy. *Cancer.* 2013;119(18):3287-3294.	Observational-Tx	575 patients	To review patients who underwent primary RP for localized prostate cancer and subsequently received salvage RT at a tertiary medical institution.	On pathologic evaluation, 563 (98%) patients had a documented GS. The median follow-up post-salvage RT was 56.7 months. A total of 60 (10.7%) patients had primary, secondary, or tertiary GP5. On univariate analysis, the presence of GP5 was prognostic for BF (HR 3.3; *P*<.0001), DM (HR: 11.1, *P*<.0001), and PCSM (HR: 8.8, *P*<.0001). Restratification of the GS to include GP5 as a distinct entity resulted in improved prognostic capability. Patients with GP5 had clinically worse outcomes than patients with GS8(4+4). On multivariate analysis, the presence of GP5 was the most adverse pathologic predictor of BF (HR 2.9; *P*<.0001), DM (HR 14.8; *P*<.0001), and PCSM (HR 5.7; *P*<.0001).	2
23. Sabolch A, Feng FY, Daignault-Newton S, et al. Gleason pattern 5 is the greatest risk factor for clinical failure and death from prostate cancer after dose-escalated radiation therapy and hormonal ablation. *Int J Radiat Oncol Biol Phys.* 2011;81(4):e351-360.	Observational-Tx	718 men	To analyze the clinical outcomes in patients treated with dose-escalated RT based on the presence or absence of GP5.	At biopsy, 89% of patients had no GP5, and 11% (76/718) had GP5. There were no differences in age, comorbid illness, T stage, PSA, or the use or duration of ADT between GS8 without GP5 and GS8-10 with GP5. The presence of GP5 predicted lower FFM (*P*<0.002; HR 3.4 [1.7–7.1]); CSS (*P*<0.0001; HR 12.9 [5.4–31]); and OS (*P*<0.0001; HR 3.6 [2.0–6.5]) in comparison with GS8 (without GP5). The 8-year FFM, CSS, and OS were 89%, 98%, and 57%, respectively, for those with Gleason 8 prostate cancer without GP5 in comparison with 61%, 55%, and 31%, respectively, for those with GP5. In addition, both FFM and CSS were strongly influenced by ADT given concurrently with RT. On multivariate analysis, GP5 was the strongest prognostic factor for all clinical endpoints, including OS.	2

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24. Mason MD, Parulekar WR, Sydes MR, et al. Final Report of the Intergroup Randomized Study of Combined Androgen-Deprivation Therapy Plus Radiotherapy Versus Androgen-Deprivation Therapy Alone in Locally Advanced Prostate Cancer. *J Clin Oncol.* 2015:[E-pub ahead of print].	Experimental-Tx	1,205 patients	To report on the longer-term survival outcomes and toxicity of a randomized trial comparing ADT alone to ADT plus RT.	1,205 patients were randomly assigned between 1995 and 2005, 602 to ADT alone and 603 to ADT+RT. At a median follow-up time of 8 years, 465 patients had died, including 199 patients from prostate cancer. OS was significantly improved in the patients allocated to ADT+RT (HR, 0.70; 95% CI, 0.57 to 0.85; *P*<.001). Deaths from prostate cancer were significantly reduced by the addition of RT to ADT (HR, 0.46; 95% CI, 0.34 to 0.61; *P*<.001). Patients on ADT+RT reported a higher frequency of adverse events related to bowel toxicity, but only 2 of 589 patients had grade 3 or greater diarrhea at 24 months after RT.	1
25. Lawton CA, DeSilvio M, Roach M, 3rd, et al. An update of the phase III trial comparing whole pelvic to prostate only radiotherapy and neoadjuvant to adjuvant total androgen suppression: updated analysis of RTOG 94-13, with emphasis on unexpected hormone/radiation interactions. *Int J Radiat Oncol Biol Phys.* 2007;69(3):646-655.	Experimental-Tx	1,292 patients	Analysis of the results of the RTOG 94-13 trial. The trial was multicenter prospective randomized and was designed to: 1.Test the hypothesis that total androgen suppression and WPRT followed by a prostate boost improves PFS by ≥10% compared with total androgen suppression and prostate only RT. 2.Test the hypothesis that NHT followed by concurrent total androgen suppression and RT improves PFS compared with RT followed by adjuvant HT by ≥10%.	The difference in OS for the 4 arms was statistically significant (*P*=0.027). However, no statistically significant differences were found in PFS or OS between NHT vs adjuvant HT and WPRT compared with prostate-only RT. A trend towards a difference was found in PFS (*P*=0.065) in favor of the WPRT + NHT arm compared with the prostate-only RT + NHT and WPRT + adjuvant HT arms.	1
26. Bolla M, de Reijke TM, Van Tienhoven G, et al. Duration of androgen suppression in the treatment of prostate cancer. *N Engl J Med.* 2009;360(24):2516-2527.	Experimental-Tx	970 randomized to short-term suppression (483) and long term suppression (487)	Randomized trial to compare the use of RT plus short-term androgen suppression with the use of RT plus long-term androgen suppression in the treatment of locally advanced prostate cancer.	Median follow-up of 6.4 years. 5-year overall mortality for short-term and long-term suppression was 19.0% and 15.2%, respectively; the observed HR was 1.42 (upper 95.71% CI, 1.79; *P*=0.65 for noninferiority). Combination of RT plus 6 months of androgen suppression provides inferior survival as compared with RT plus 3 years of androgen suppression in the treatment of locally advanced prostate cancer.	1
27. D'Amico AV, Chen MH, Renshaw AA, Loffredo M, Kantoff PW. Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. *JAMA.* 2008;299(3):289-295.	Experimental-Tx	206 men	Randomized trial to compare 6 months of AST and RT to RT alone and to assess the interaction between level of comorbidity and all-cause mortality.	Median follow-up was 7.6 years. Addition of 6 months of AST to RT resulted in increased OS in men with localized but unfavorable-risk prostate cancer.	1

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28. Denham JW, Steigler A, Lamb DS, et al. Short-term neoadjuvant androgen deprivation and radiotherapy for locally advanced prostate cancer: 10-year data from the TROG 96.01 randomised trial. *Lancet Oncol.* 2011;12(5):451-459.	Experimental-Tx	818 men	To report results of the TROG 96.01 trial, which assessed whether 3-month and 6-month short-term NADT decreases clinical progression and mortality after RT for locally advanced prostate cancer.	802 men were eligible for analysis (270 in the RT alone group, 265 in the 3-month NADT group, and 267 in the 6-month NADT group) after a median follow-up of 10.6 years (IQR 6.9–11.6). Compared with RT alone, 3 months of NADT decreased the cumulative incidence of PSA progression (adjusted HR 0.72, 95% CI 0.57–0.90; *P*=0.003) and local progression (0.49, 0.33–0.73; *P*=0.0005), and improved event-free survival (0.63, 0.52–0.77; *P*<0.0001). 6 months of NADT further reduced PSA progression (0.57, 0.46–0.72; *P*<0.0001) and local progression (0.45, 0.30–0.66; *P*=0.0001), and led to a greater improvement in event-free survival (0.51, 0.42–0.61, *P*<0.0001), compared with RT alone. 3-month NADT had no effect on distant progression (0.89, 0.60–1.31; *P*=0.550), PCSM (0.86, 0.60–1.23; *P*=0.398), or all-cause mortality (0.84, 0.65–1.08; *P*=0.180), compared with RT alone. By contrast, 6-month NADT decreased distant progression (0.49, 0.31–0.76; *P*=0.001), PCSM (0.49, 0.32–0.74; *P*=0.0008), and all-cause mortality (0.63, 0.48–0.83; *P*=0.0008), compared with RT alone. Treatment-related morbidity was not increased with NADT within the first 5 years after randomization.	1
29. Horwitz EM, Bae K, Hanks GE, et al. Ten-year follow-up of radiation therapy oncology group protocol 92-02: a phase III trial of the duration of elective androgen deprivation in locally advanced prostate cancer. *J Clin Oncol.* 2008;26(15):2497-2504.	Experimental-Tx	1,554 patients	To determine whether adding 2 years of ADT improved outcome for patients electively treated with ADT before and during RT.	Median follow-up of all survival patients is 11.31 and 11.27 years for the 2 arms. At 10 years, the long-term ADT + RT group showed significant improvement over the short-term ADT + RT group for all end points except OS: DFS (13.2% vs 22.5%; *P*<.0001), disease-specific survival (83.9% vs 88.7%; *P*=.0042), local progression (22.2% vs 12.3%; *P*<.0001), distant metastasis (22.8% vs 14.8%; *P*<.0001), BF (68.1% v 51.9%; *P*≤.0001), and OS (51.6% vs 53.9%, *P*=.36). One subgroup analyzed consisted of all cancers with a GS of 8 to 10 cancers. An OS difference was observed (31.9% vs 45.1%; *P*=.0061), as well as in all other end points herein.	1

Locally Advanced, High-Risk Prostate Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
30. Zapatero A, Guerrero A, Maldonado X, et al. High-dose radiotherapy with short-term or long-term androgen deprivation in localised prostate cancer (DART01/05 GICOR): a randomised, controlled, phase 3 trial. *Lancet Oncol.* 2015;16(3):320-327.	Experimental-Tx	355 patients	To determine whether long-term ADT was superior to short-term ADT when combined with high-dose RT.	Between Nov 7, 2005, and Dec 20, 2010, 178 patients were randomly assigned to receive short-term ADT and 177 to receive long-term ADT. After a median follow-up of 63 months (IQR 50-82), 5-year biochemical DFS was significantly better among patients receiving long-term ADT than among those receiving short-term treatment (90% [95% CI, 87–92] vs 81% [78–85]; HR 1.88 [95% CI, 1.12–3.15]; *P*=0.01). 5-year OS (95% [95% CI, 93–97] vs 86% [83–89]; HR 2.48 [95% CI, 1.31–4.68]; *P*=0.009) and 5-year metastasis-free survival (94% [95% CI, 92–96] vs 83% [80–86]; HR 2.31 [95% CI, 1.23–3.85]; *P*=0.01) were also significantly better in the long-term ADT group than in the short-term ADT group. The effect of long-term ADT on biochemical DFS, metastasis-free survival, and OS was more evident in patients with high-risk disease than in those with low-risk disease. Grade 3 late rectal toxicity was noted in 3 (2%) of 177 patients in the long-term ADT group and 2 (1%) of 178 in the short-term ADT group; grade 3-4 late urinary toxicity was noted in 5 (3%) patients in each group. No deaths related to treatment were reported.	1
31. Pisansky TM, Suman VJ, Roach M, 3rd, Sandler HM. Reporting of results in DART01/05 GICOR. *Lancet Oncol.* 2015;16(6):e258.	Review/Other-Tx	N/A	No abstract available.	No abstract available.	4

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
32. Nabid A, Carrier N, Martin A-G, et al. High-risk prostate cancer treated with pelvic radiotherapy and 36 versus 18 months of androgen blockade: Results of a phase III randomized study. *ASCO Meeting Abstracts.* 2013;31(6_suppl):3.	Experimental-Tx	630 patients	To compare outcomes between 36 vs 18 months of androgen blockade in high risk prostate cancer treated with RT.	From October 2000 to January 2008, 310 patients were randomized to arm 1 and 320 to arm 2. Patients' characteristics were well balanced between the 2 arms (median age 71 years, median PSA 16 ng/mL, median GS 8). Most patients had T2-3 disease. At a median follow-up of 77 months, 71/310 patients (22.9%) in arm 1 and 76/320 (23.8%) in arm 2 had died (P=0.802). Overall, 116 patients died of causes other than prostate cancer. Overall and cancer specific survival HRs were 1.15 (0.83–1.59), P=0.398 and 1.13 (0.61–2.08), P=0.153, respectively. 5 year overall and disease specific survival rates were 92.1% (89.1–95.1) vs 86.8% (83.0–90.6), P=0.052 and 97.6% (95.9–99.4) vs 96.4% (94.2–98.6), P=0.473 and 10 year overall and disease specific survival rates were 63.6% (55.7–71.5) vs 63.2% (54.7–71.7), P=0.429 and 87.2% (81.0–93.3) vs 87.2% (80.9–93.6), P=0.838 for arm 1 and arm 2, respectively. There were no significant differences in the rates of biochemical, regional or distant failure between arms.	1
33. Pommier P, Chabaud S, Lagrange JL, et al. Is there a role for pelvic irradiation in localized prostate adenocarcinoma? Preliminary results of GETUG-01. *J Clin Oncol.* 2007;25(34):5366-5373.	Experimental-Tx	446 patients	Review of a randomized multicenter open phase III trial to assess the benefit and toxicity and QoL outcomes of pelvic nodes irradiation in nonmetastatic prostate carcinoma patients. Patients were randomly assigned to either pelvic and prostate RT or prostate RT only.	With a 42.1-month median follow-up time, the 5-year PFS and OS were similar in the 2 treatment arms for the whole series and for each stratified group. On multivariate analysis, low lymph node involvement risk and HT were statistically associated with increased PFS. However, subgroup analyses based on these factors did not show any benefit for pelvic irradiation. There were no significant differences in acute and late digestive toxicities and in QoL outcomes.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
34. Rusthoven CG, Carlson JA, Waxweiler TV, et al. The impact of definitive local therapy for lymph node-positive prostate cancer: a population-based study. *Int J Radiat Oncol Biol Phys.* 2014;88(5):1064-1073.	Observational-Tx	796 cN+ and 2,991 pN+ patients	To evaluate the survival outcomes for patients with lymph node-positive, nonmetastatic prostate cancer undergoing definitive local therapy (RP, EBRT, or both) vs no local therapy in the U.S. population in the modern PSA era.	Among cN+ patients, 43% underwent EBRT and 57% had no local therapy. Outcomes for cN+ patients favored EBRT, with 10-year OS rates of 45% vs 29% (*P*<.001) and prostate cancer-specific survival rates of 67% vs 53% (*P*<.001). Among pN+ patients, 78% underwent local therapy (RP 57%, EBRT 10%, or both 11%) and 22% had no local therapy. Outcomes for pN+ also favored local therapy, with 10-year OS rates of 65% vs 42% (*P*<.001) and prostate cancer-specific survival rates of 78% vs 56% (*P*<.001). On multivariate analysis, local therapy in both the cN+ and pN+ cohorts remained independently associated with improved OS and prostate cancer-specific survival (all *P*<.001). Local therapy was associated with favorable HRs across subgroups, including patients aged ≥70 years and those with multiple positive lymph nodes. Among pN+ patients, no significant differences in survival were observed between RP vs EBRT and RP with or without adjuvant EBRT.	2
35. Johnstone PA, Assikis V, Goodman M, Ward KC, Riffenburgh RH, Master V. Lack of survival benefit of post-operative radiation therapy in prostate cancer patients with positive lymph nodes. *Prostate Cancer Prostatic Dis.* 2007;10(2):185-188.	Observational-Tx	1,921 patients	To provide for informed decisions as to whether RT post-RP benefits the +lymph nodes patient.	Specifically analyzed were data for 1,921 patients with nonmetastatic prostate cancer who underwent surgery alone, or surgery followed by RT, and who had +lymph nodes documented. SEER does not code the interval between surgery and RT, so the ratio of patients receiving salvage vs adjuvant therapy is unknown. Using follow-up data through 2002, post-diagnosis survival was examined by number of +lymph nodes. There was no significant relative survival benefit for +lymph node patients receiving postoperative RT (chi(2)*P*=0.270).	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
36. Briganti A, Karnes RJ, Da Pozzo LF, et al. Combination of adjuvant hormonal and radiation therapy significantly prolongs survival of patients with pT2-4 pN+ prostate cancer: results of a matched analysis. *Eur Urol.* 2011;59(5):832-840.	Observational-Tx	703 patients	To assess the impact of combination adjuvant HT and RT on the survival of patients with prostate cancer and histologically documented lymph node metastases (pN+).	Following the matching process, 117 pT2-4 pN1 patients of 171 (68.4%) treated with adjuvant HT plus RT (group 1) were compared with 247 pT2-4 pN1 patients of 532 (46.4%) receiving adjuvant HT alone (group 2). After matching, the 2 groups of patients were comparable in terms of pre- and postoperative characteristics (all $P \geq 0.07$). Mean follow-up was 100.8 mo (median: 95.1 mo; range: 3.5–229.3 mo). Overall, prostate CSS and OS rates at 5, 8, and 10 years were 90%, 82%, and 75%, and 85%, 70%, and 60%, respectively. Patients treated with ART plus HT had significantly higher CSS and OS rates compared with patients treated with HT alone at 5, 8, and 10 years after surgery (95%, 91%, and 86% vs 88%, 78%, and 70%, and 90%, 84%, and 74% vs 82%, 65%, and 55%, respectively; $P=0.004$ and $P<0.001$, respectively). Similarly, higher survival rates associated with the combination of HT plus RT were found when patients were stratified according to the extent of nodal invasion (namely, 2 or fewer vs more than 2 positive nodes; all $P \leq 0.006$). Lack of standardized HT and RT protocols represents the main limitations of our retrospective study.	2
37. Abdollah F, Karnes RJ, Suardi N, et al. Impact of adjuvant radiotherapy on survival of patients with node-positive prostate cancer. *J Clin Oncol.* 2014;32(35):3939-3947.	Observational-Tx	1,107 patients	To test the hypothesis that the impact of ART on cancer-specific mortality in patients with pN1 prostate cancer is related to tumor characteristics.	Overall, 35% of patients received ART. At multivariable analysis, ART was associated with more favorable cancer-specific mortality rate (HR, 0.37; $P<.001$). However, when patients were stratified into risk groups, only 2 groups of men benefited from ART: (1) patients with positive lymph node count ≤2, GS 7 to 10, pT3b/pT4 stage, or positive surgical margins (HR, 0.30; $P=.002$); and (2) patients with positive lymph node count of 3 to 4 (HR, 0.21; $P=.02$), regardless of other tumor characteristics. These results were confirmed when overall mortality was examined as an end point.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
38. Kuban DA, Tucker SL, Dong L, et al. Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. *Int J Radiat Oncol Biol Phys.* 2008;70(1):67-74.	Experimental-Tx	301 patients	To report the long-term results of a randomized RT dose escalation trial for prostate cancer.	For all patients, FFbF or clinical failure was superior for the 78 Gy arm, 78%, as compared with 59% for the 70 Gy arm (P=0.004, and an even greater benefit was seen in patients with initial PSA >10 ng/mL (78% vs 39%, P=0.001). Clinical failure rate was significantly reduced in the 78 Gy arm as well (7% vs 15%, P=0.014).	1
39. Spratt DE, Pei X, Yamada J, Kollmeier MA, Cox B, Zelefsky MJ. Long-term survival and toxicity in patients treated with high-dose intensity modulated radiation therapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys.* 2013;85(3):686-692.	Experimental-Tx	1,002 patients; 587 patients treated with neoadjuvant and concurrent ADT	To report long-term survival and toxicity outcomes with the use of high-dose IMRT to 86.4 Gy for patients with localized prostate cancer.	For low-, intermediate-, and high-risk groups, 7-year biochemical relapse-free survival outcomes were 98.8%, 85.6%, and 67.9%, respectively (P<.001), and distant metastasis-free survival rates were 99.4%, 94.1%, and 82.0% (P<.001), respectively. On multivariate analysis, T stage (P<.001), GS (P<.001), and >50% of initial biopsy positive core (P=.001) were predictive for DM. No prostate cancer-related deaths were observed in the low-risk group. The 7-year PCSM rates, using competing risk analysis for intermediate- and high-risk groups, were 3.3% and 8.1%, respectively (P=.008). On multivariate analysis, GS (P=.004), percentage of biopsy core positivity (P=.003), and T-stage (P=.033) were predictive for PCSM. Actuarial 7-year grade 2 or higher late gastrointestinal and genitourinary toxicities were 4.4% and 21.1%, respectively. Late grade 3 gastrointestinal and genitourinary toxicity was experienced by 7 patients (0.7%) and 22 patients (2.2%), respectively. Of the 427 men with full potency at baseline, 317 men (74%) retained sexual function at time of last follow-up.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
40. Arcangeli S, Strigari L, Gomellini S, et al. Updated results and patterns of failure in a randomized hypofractionation trial for high-risk prostate cancer. *Int J Radiat Oncol Biol Phys.* 2012;84(5):1172-1178.	Experimental-Tx	168 patients	To report long-term results and patterns of failure after conventional and hypofractionated RT in high-risk prostate cancer.	In a median follow-up of 70 months, BF occurred in 35/168 patients (21%) in the study. Among these 35 patients, local failure only was detected in 11 (31%), distant failure only in 16 (46%), and both local failure and distant failure in 6 (17%). In 2 patients (6%) BF has not yet been clinically detected. The risk reduction by hypofractionation was significant in BF (10.3%) but not in local failure and distant failure. We found that hypofractionation, with respect to conventional fractionation, determined only an insignificant increase in the actuarial FFbF but no difference in freedom from local failure and freedom from distant failure, when considering the entire group of patients. However, an increase in the 5-year rates in all 3 endpoints-FFbF, freedom from local failure, and freedom from distant failure -was observed in the subgroup of patients with a pretreatment PSA level of 20 ng/mL or less. On multivariate analysis, the type of fractionation, pretreatment PSA level, GS of 4+3 or higher, and T stage of 2c or higher have been confirmed as independent prognostic factors for BF. High pretreatment PSA levels and GS of 4+3 or higher were also significantly associated with an increased risk of distant failure, whereas T stage of 2c or higher was the only independent variable for local failure.	1
41. Patel AR, Sandler HM, Pienta KJ. Radiation Therapy Oncology Group 0521: a phase III randomized trial of androgen suppression and radiation therapy versus androgen suppression and radiation therapy followed by chemotherapy with docetaxel/prednisone for localized, high-risk prostate cancer. *Clin Genitourin Cancer.* 2005;4(3):212-214.	Review/Other-Tx	N/A	A treatment plan to determine whether cytotoxic chemotherapy will add to the control rates obtained with RT plus androgen suppression alone.	No results reported in abstract.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
42. Rosenthal SA, Bae K, Pienta KJ, et al. Phase III multi-institutional trial of adjuvant chemotherapy with paclitaxel, estramustine, and oral etoposide combined with long-term androgen suppression therapy and radiotherapy versus long-term androgen suppression plus radiotherapy alone for high-risk prostate cancer: preliminary toxicity analysis of RTOG 99-02. *Int J Radiat Oncol Biol Phys.* 2009;73(3):672-678.	Experimental-Tx	381 patients: 192 – Arm 1; 189 – Arm 2	To determine whether adjuvant chemotherapy with paclitaxel, estramustine, and etoposide plus AST + RT would improve disease outcomes with acceptable toxicity.	136 Arm 2 patients (71%) had RTOG Grade 3 or greater toxicity compared with 70 Arm 1 patient (37%). Statistically significant increases in hematologic toxicity ($P<0.0001$) and gastrointestinal toxicity ($P=0.017$) but not genitourinary toxicity ($P=0.07$) were noted during treatment. Two Grade 5 complications related to neutropenic infection occurred in Arm 2. Three cases of myelodysplasia/acute myelogenous leukemia were noted in Arm 2. At 2 and 3 years after therapy completion, excess long-term toxicity was not observed in Arm 2. Paclitaxel, estramustine, and etoposide were associated with significantly increased toxicity during treatment. The toxicity profiles did not differ at 2 and 3 years after therapy. Toxicity is an important consideration in the design of trials using adjuvant chemotherapy for prostate cancer.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
43. Kupelian PA, Potters L, Khuntia D, et al. Radical prostatectomy, external beam radiotherapy <72 Gy, external beam radiotherapy > or =72 Gy, permanent seed implantation, or combined seeds/external beam radiotherapy for stage T1-T2 prostate cancer. *Int J Radiat Oncol Biol Phys.* 2004;58(1):25-33.	Observational-Tx	2991 patients	To review the biochemical relapse-free survival rates after treatment with permanent seed implantation (PI), EBRT <72 Gy (EBRT <72), EBRT ≥72 Gy (EBRT ≥72), combined seeds and EBRT, or RP for clinical stage T1-T2 localized prostate cancer treated between 1990 and 1998.	The 5-year biochemical relapse-free survival rate for RP, EBRT <72, EBRT ≥72, permanent seed implantation, and combined seeds and EBRT was 81%, 51%, 81%, 83%, and 77%, respectively (P<0.001). The 7-year biochemical relapse-free survival rate for RP, EBRT <72, EBRT ≥72, permanent seed implantation, and combined seeds and EBRT was 76%, 48%, 81%, 75%, and 77%, respectively. Multivariate analysis, including all cases, showed pretreatment PSA (P<0.001), biopsy GS (P<0.001), year of therapy (P<0.001), and treatment modality (P<0.001) to be independent predictors of relapse. Because EBRT <72 cases had distinctly worse outcomes, the analysis was repeated after excluding these cases to discern any differences among the other modalities. The multivariate analysis excluding the EBRT <72 cases revealed pretreatment PSA (P<0.001), biopsy GS (P<0.001), and year of therapy (P= 0.001) to be the only independent predictors of relapse. Treatment modality (P=0.95), clinical T stage (P=0.09), and ADT (P=0.56) were not independent predictors for failure.	2
44. Westover K, Chen MH, Moul J, et al. Radical prostatectomy vs radiation therapy and androgen-suppression therapy in high-risk prostate cancer. *BJU Int.* 2012;110(8):1116-1121.	Observational-Tx	657 patients	To assess the risk of PCSM after therapy with RP or combined-modality therapy with brachytherapy, EBRT and AST in men with GS 8-10 prostate cancer.	As of January 2009, with a median (IQR) follow-up of 4.62 (2.4–8.2) years, there were 21 prostate cancer-specific deaths. Treatment with RP was not associated with an increased risk of PCSM compared with combined-modality therapy (adjusted HR 1.8, 95% CI, 0.6–5.6, P=0.3). Factors associated with an increased risk of PCSM were a PSA concentration of <4 ng/mL (adjusted HR 6.1, 95% CI, 2.3–16, P<0.001) as compared with ≥4 ng/mL, and clinical category T2b, c (adjusted HR 2.9; 95% CI, 1.1–7.2; P=0.03) as compared with T1c, 2a.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
45. Aizer AA, Yu JB, Colberg JW, McKeon AM, Decker RH, Peschel RE. Radical prostatectomy vs. intensity-modulated radiation therapy in the management of localized prostate adenocarcinoma. *Radiother Oncol.* 2009;93(2):185-191.	Observational-Tx	556 patients RP (n=204) or IMRT (n=352)	To determine whether RP or IMRT to ≥72 Gy, plus HT if indicated, results in improved biochemical DFS in localized prostate adenocarcinoma.	IMRT patients had more advanced disease at baseline (*P*<.001). There was no difference in 5-year biochemical DFS rates between RP and IMRT in the favorable (92.8% vs 85.3%, *P*=.20) or intermediate prognosis (86.7% vs 82.2%, *P*=.46) subsets. A difference favoring IMRT plus HT was seen in the poor prognosis (38.4% vs 62.2%, *P*<.001) subset. Within the entire cohort, after adjustment for confounding variables, GS (*P*<.001) and clinical stage (*P*<.001) predicted biochemical DFS, but treatment modality (*P*=.06) did not. Within the poor prognosis subset, treatment modality (*P*=.006) predicted biochemical DFS.	2
46. Ellis CL, Partin AW, Han M, Epstein JI. Adenocarcinoma of the prostate with Gleason score 9-10 on core biopsy: correlation with findings at radical prostatectomy and prognosis. *J Urol.* 2013;190(6):2068-2073.	Observational-Tx	259 men	To report the largest study to date to specifically analyze the correlation of GS 9-10 on needle core biopsy with RP outcomes.	Statistically significant predictors of RP outcome were organ confinement (total cores with GS 9-10, maximum percent overall and PNI), margin status (preoperative PSA and clinical stage), seminal vesicle invasion (maximum percent overall, PNI and clinical stage), lymph node metastasis (total number of cores with GS 9-10 and clinical stage) and biochemical-free survival (maximum percent of GS 9-10, maximum percent overall and clinical stage) (each *P*<0.05).	2
47. Cooperberg MR, Vickers AJ, Broering JM, Carroll PR. Comparative risk-adjusted mortality outcomes after primary surgery, radiotherapy, or androgen-deprivation therapy for localized prostate cancer. *Cancer.* 2010;116(22):5226-5234.	Observational-Tx	7,538 patients	To analyze risk-adjusted, cancer-specific mortality outcomes among men who underwent RP, men who received EBRT, and men who received primary ADT.	In total, 266 men died of prostate cancer during follow-up. Adjusting for age and risk, the HR for cancer-specific mortality relative to prostatectomy was 2.21 (95% CI, 1.50–3.24) for RT and 3.22 (95% CI, 2.16–4.81) for ADT. Absolute differences between prostatectomy and RT were small for men at low risk but increased substantially for men at intermediate and high risk. These results were robust to a variety of different analytic techniques, including competing risks regression analysis, adjustment by CAPRA score rather than Kattan score, and examination of OS as the endpoint.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
48. Hoffman RM, Koyama T, Fan KH, et al. Mortality after radical prostatectomy or external beam radiotherapy for localized prostate cancer. *J Natl Cancer Inst.* 2013;105(10):711-718.	Observational-Tx	1,164 RP patients; 491 EBRT patients	To estimate the association of RP (compared with EBRT) with overall and prostate cancer mortality.	After 15 years of follow-up, there were 568 deaths, including 104 from prostate cancer. RP was associated with statistically significant advantages for overall (HR = 0.60, 95% CI = 0.53 to 0.70, *P*<.0001.) and disease-specific mortality (HR = 0.35, 95% CI = 0.26 to 0.49, *P*<.0001.). Mortality benefits for RP were also observed within treatment propensity quintiles, when subjects were pair-matched on propensity scores, and in subgroup analyses based on age, tumor characteristics, and comorbidity.	2
49. Kibel AS, Ciezki JP, Klein EA, et al. Survival among men with clinically localized prostate cancer treated with radical prostatectomy or radiation therapy in the prostate specific antigen era. *J Urol.* 2012;187(4):1259-1265.	Observational-Tx	10,429 patients	To analyze the survival of patients treated with RP, EBRT and brachytherapy according to contemporary standards.	The adjusted 10-year OS after RP, EBRT and brachytherapy was 88.9%, 82.6% and 81.7%, respectively. Adjusted 10-year PCSM was 1.8%, 2.9% and 2.3%, respectively. Using propensity score analysis, EBRT was associated with decreased OS (HR 1.6, 95% CI, 1.4–1.9, *P*<0.001) and increased PCSM (HR 1.5, 95% CI, 1.0–2.3, *P*=0.041) compared to RP. Brachytherapy was associated with decreased OS (HR 1.7, 95% CI, 1.4–2.1, *P*<0.001) but not PCSM (HR 1.3, 95% CI, 0.7–2.4, *P*=0.5) compared to RP.	2
50. Nepple KG, Stephenson AJ, Kallogjeri D, et al. Mortality after prostate cancer treatment with radical prostatectomy, external-beam radiation therapy, or brachytherapy in men without comorbidity. *Eur Urol.* 2013;64(3):372-378.	Observational-Tx	6,692 patients	To evaluate prostate cancer mortality and overall mortality in men with no recorded comorbidity treated with RP, EBRT, or brachytherapy.	Using Cox analysis, EBRT was associated with an increase in prostate cancer mortality compared with RP (HR: 1.66; 95% CI, 1.05–2.63), while there was no statistically significant increase with brachytherapy (HR: 1.83; 95% CI, 0.88–3.82). Using competing risks analysis, the benefit of RP remained but was no longer statistically significant for EBRT (HR: 1.55; 95% CI, 0.92–2.60) or brachytherapy (HR: 1.66; 95% CI, 0.79–3.46). In comparison with RP, both EBRT (HR: 1.71; 95% CI, 1.40–2.08) and brachytherapy (HR: 1.78; 95% CI, 1.37–2.31) were associated with increased overall mortality.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
51. Sooriakumaran P, Nyberg T, Akre O, et al. Comparative effectiveness of radical prostatectomy and radiotherapy in prostate cancer: observational study of mortality outcomes. *BMJ.* 2014;348:g1502.	Observational-Tx	34,515 patients	To compare the survival outcomes of patients treated with surgery or RT for prostate cancer.	Prostate cancer mortality became a larger proportion of overall mortality as risk group increased for both the surgery and the RT cohorts. Among patients with nonmetastatic prostate cancer the adjusted subdistribution HR for prostate cancer mortality favored surgery (1.76, 95% CI, 1.49 to 2.08, for RT vs prostatectomy), whereas there was no discernible difference in treatment effect among men with metastatic disease. Subgroup analyses indicated more clear benefits of surgery among younger and fitter men with intermediate and high risk disease. Sensitivity analyses confirmed the main findings.	2
52. Briganti A, Joniau S, Gontero P, et al. Identifying the best candidate for radical prostatectomy among patients with high-risk prostate cancer. *Eur Urol.* 2012;61(3):584-592.	Observational-Tx	1,366 patients	To identify which high-risk prostate cancer patients might have favorable pathologic outcomes when surgically treated.	Overall, 505/1,366 patients (37%) had specimen-confined disease at RP. All preoperative variables (ie, age and PSA at surgery, clinical stage, and biopsy Gleason sum) were independent predictors of specimen-confined prostate cancer at RP (all $P \leq 0.04$). Patients with specimen-confined disease had significantly higher 10-year BCR-free survival and CSS rates than patients without specimen-confined disease at RP (66% vs 47% and 98 vs 88%, respectively; all $P < 0.001$). A nomogram including PSA, age, clinical stage, and biopsy Gleason sum demonstrated 72% accuracy in predicting specimen-confined prostate cancer. This study is limited by its retrospective design and by the lack of an external validation of the nomogram.	2
53. Gustafson GS, Nguyen PL, Assimos DG, et al. ACR Appropriateness Criteria(R) Postradical Prostatectomy Irradiation in Prostate Cancer. *Oncology (Williston Park).* 2014;28(12).	Review/Other-Tx	N/A	Evidence-based guidelines to assist referring physicians and other providers in making the most appropriate treatment decisions for postradical prostatectomy irradiation in prostate cancer.	N/A	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
54. Grimm P, Billiet I, Bostwick D, et al. Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy. Results from the Prostate Cancer Results Study Group. *BJU Int.* 2012;109 Suppl 1:22-29.	Review/Other-Tx	N/A	A comprehensive review of the literature comparing risk stratified patients by treatment option and with long-term follow-up.	A statistical analysis (standard deviational ellipse) of the study outcomes suggested that, in terms of biochemical-free progression, brachytherapy provides superior outcome in patients with low-risk disease. For intermediate-risk disease, the combination of EBRT and brachytherapy appears equivalent to brachytherapy alone. For high-risk patients, combination therapies involving EBRT and brachytherapy plus or minus ADT appear superior to more localized treatments such as seed implant alone, surgery alone or EBRT.	4
55. Shilkrut M, Merrick GS, McLaughlin PW, et al. The addition of low-dose-rate brachytherapy and androgen-deprivation therapy decreases biochemical failure and prostate cancer death compared with dose-escalated external-beam radiation therapy for high-risk prostate cancer. *Cancer.* 2013;119(3):681-690.	Observational-Tx	958 patients	To determine whether the addition of low-dose-rate brachytherapy or androgen-deprivation therapy improves clinical outcome in patients with high-risk prostate cancer who received dose-escalated RT.	The median follow-up was 63.2 months (IQR, 35.4–99.0 months), and 250 patients were followed for >8 years. Compared with combined modality therapy, patients who received EBRT had higher PSA levels, higher tumor classification, lower Gleason sum, and more frequent receipt of ADT for a longer duration. The 8-year incidence BF and PCSM among patients who received EBRT was 40% (standard error, 38%–44%) and 13% (standard error, 11%–15%) compared with 14% (standard error, 12%–16%; $P<.0001$) and 7% (standard error 6%–9%; $P=.003$) among patients who received combined modality therapy. On multivariate analysis, the HRs for BF and PCSM were 0.35 (95% CI, 0.23–0.52; $P<.0001$) and 0.41 (95% CI, 0.23–0.75; $P<.003$), favoring combined modality therapy. Increasing duration of ADT predicted decreased BF ($P=.04$) and PCSM ($P=.001$), which was greatest with long-term ADT (BF: HR, 0.33; $P<.0001$; 95% CI, 0.21–0.52; PCSM: HR, 0.30; $P=.001$; 95% CI, 0.15–0.6) even in the subgroup that received combined modality therapy.	2

Locally Advanced, High-Risk Prostate Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
56. Taira AV, Merrick GS, Galbreath RW, et al. Distant metastases following permanent interstitial brachytherapy for patients with clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys.* 2012;82(2):e225-232.	Observational-Tx	1,840 consecutive patients	To compare metastases-free survival or CSS between men treated with RP vs those treated with brachytherapy in a consecutive cohort of patients undergoing permanent interstitial brachytherapy.	For the entire cohort, metastases-free survival and CSS at 12 years were 98.1% and 98.2%, respectively. When rates were stratified by low, intermediate, and high-risk groups, the 12-year metastases-free survival was 99.8%, 98.1%, and 93.8% (P<0.001), respectively. CSS rates were 99.8%, 98.0%, and 95.3% (P<0.001) for low, intermediate, and high-risk groups, respectively. bPFS was 98.7%, 95.9% and 90.4% for low, intermediate, and high-risk patients, respectively (P<0.001). In multivariate Cox-regression analysis, metastases-free survival was mostly closely related to GS and year of treatment, whereas CSS was most closely associated with GS.	2
57. Merrick GS, Butler WM, Galbreath RW, et al. Prostate cancer death is unlikely in high-risk patients following quality permanent interstitial brachytherapy. *BJU Int.* 2011;107(2):226-232.	Observational-Tx	284 patients	To evaluate CSS, bPFS and OS in high-risk prostate cancer brachytherapy patients.	12-year CSS, bPFS and OS were 94.2%, 89.0% and 69.7%. On multivariate analysis, bPFS was best predicted by percent positive biopsies and ADT. The analysis failed to identify any predictors for CSS, while OS was highly correlated with patient age, percent positive biopsies and diabetes. 14% of patients died from diseases of the heart, while 8%, 8% and 6% of patients died from nonprostate cancer, other causes and prostate cancer, respectively. When OS was stratified by patients with 0-3 vs ≥4 comorbidities, the 12-year OS was 73.0% and 52.7% (P=0.036).	2

Locally Advanced, High-Risk Prostate Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
58. Morris WJ, Tyldesley S, Pai HH, et al. ASCENDE-RT*: A multicenter, randomized trial of dose-escalated external beam radiation therapy (EBRT-B) versus low-dose-rate brachytherapy (LDR-B) for men with unfavorable-risk localized prostate cancer. *J Clin Oncol.* 2015;33:(suppl 7; abstr 3).	Experimental-Tx	398 patients	To compare the efficacy of dose-escalated EBRT and low-dose-rate brachytherapy for NCCN high- and intermediate-risk disease.	Between Dec 2002 and Sep 2011, 276 high-risk and 122 intermediate-risk patients were accrued at 6 cancer treatment centers. 200 men were assigned to dose-escalated EBRT and 198 to low-dose-rate brachytherapy. The treatment arms were well balanced in terms of age and known prognostic factors. Median follow-up is 6.5 years; 65 men have >9 years follow-up. There were 12 major protocol violations in each arm. By intent-to-treat analysis, the 3-, 5-, 7-, and 9-year Kaplan-Meier relapse-free survival estimates are 94% vs 94%, 77% vs 89%, 71% vs 86%, and 63% vs 83% for dose-escalated EBRT and low-dose-rate brachytherapy respectively (HR = 0.473; 95% CI, 0.292–0.765; *P*=0.0022). Randomization (*P*<0.001), percent positive cores (*P*=0.005), initial PSA (*P*=0.006) and clinical T-stage (*P*=0.013) were predictive of relapse-free survival in a multivariable Cox model. The median PSA at latest follow-up for nonrelapsing patients assigned to low-dose-rate brachytherapy is 0.02 vs 0.24 ng/mL for dose-escalated EBRT.	1
59. D'Amico AV, Moran BJ, Braccioforte MH, et al. Risk of death from prostate cancer after brachytherapy alone or with radiation, androgen suppression therapy, or both in men with high-risk disease. *J Clin Oncol.* 2009;27(24):3923-3928.	Observational-Tx	1,342 men	To estimate the risk of PCSM after brachytherapy alone or in conjunction with AST, EBRT, or both in men with high-risk prostate cancer.	Despite higher baseline probabilities of PCSM after a median follow-up of 5.1 years, there was a significant reduction in the risk of PCSM (adjusted HR, 0.32; 95% CI, 0.14 to 0.73; *P*=.006) in men treated with brachytherapy and both AST and EBRT as compared with neither. When compared with brachytherapy alone, a significant decrease in the risk of PCSM was not observed in men treated with either supplemental AST (adjusted HR, 0.63; 95% CI, 0.27 to 1.47; *P*=.28) or EBRT (adjusted HR, 0.57; 95% CI, 0.21 to 1.52; *P*=.26). There was a near-significant reduction (adjusted HR, 0.53; 95% CI, 0.27 to 1.07; *P*=.079) in the risk of PCSM in men treated with tri- as compared with bimodality therapy.	2

Locally Advanced, High-Risk Prostate Cancer
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
60. Deutsch I, Zelefsky MJ, Zhang Z, et al. Comparison of PSA relapse-free survival in patients treated with ultra-high-dose IMRT versus combination HDR brachytherapy and IMRT. *Brachytherapy.* 2010;9(4):313-318.	Observational-Tx	630 total patients treated with dose escalated RT; 160 treated with IMRT of 50.4 Gy; 470 treated with IMRT of 86.4 Gy	A retrospective comparison of biochemical outcomes using an ultra-high dose of conventionally fractionated IMRT vs a lower dose of IMRT combined with HDR brachytherapy to increase the biologically effective dose of IMRT.	The 5-year actuarial PSA relapse-free survival for HDR plus IMRT vs ultra-high-dose IMRT were 100% vs 98%, 98% vs 84%, and 93% vs 71%, for NCCN low- (P=0.71), intermediate- (P<0.001), and high-risk (P=0.23) groups, respectively. Treatment (P=0.0006), T stage (P<0.0001), GS (P<0.0001), pretreatment PSA (P=0.0037), risk group (P<0.0001), and lack of ADT (P=0.0005) were significantly associated with improved PSA relapse-free survival on univariate analysis. HDR plus IMRT vs ultra-high-dose IMRT (P=0.0012, HR=0.184); age (P=0.0222, HR=0.965); and risk group (P<0.0001, HR=2.683) were associated with improved PSA relapse-free survival on multivariate analysis. Dose escalation of IMRT by adding HDR brachytherapy provided improved PSA relapse-free survival in the treatment of prostate cancer compared with ultra-high-dose IMRT, independent of risk group on multivariate analysis, with the most significant benefit for intermediate-risk patients.	2
61. Hoffman KE, Chen MH, Moran BJ, et al. Prostate cancer-specific mortality and the extent of therapy in healthy elderly men with high-risk prostate cancer. *Cancer.* 2010;116(11):2590-2595.	Observational-Tx	764 patients: 206 received brachytherapy alone; 558 received AST	Compare the use of brachytherapy alone with combined brachytherapy, EBRT to the prostate and seminal vesicles, and AST in a population of healthy elderly men.	After adjusting for age and prostate cancer prognostic factors, risk of PCSM was significantly less for men who received AST than those receiving brachytherapy alone. Other factors associated significantly with an increased risk of PCSM included GS of 8-10. Elderly men who had high-risk prostate cancer without cardiovascular disease or with surgically corrected cardiovascular disease had lower risk of PCSM when they received AST than brachytherapy alone. These results support aggressive locoregional treatment in healthy elderly men with high-risk prostate cancer.	2

Locally Advanced, High-Risk Prostate Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
62. Cohen JK, Miller RJ, Jr., Ahmed S, Lotz MJ, Baust J. Ten-year biochemical disease control for patients with prostate cancer treated with cryosurgery as primary therapy. *Urology.* 2008;71(3):515-518.	Observational-Tx	370 patients	To report the long-term biochemical and biopsy follow-up for a cohort of patients who had undergone prostate cryosurgery as primary treatment of prostate adenocarcinoma.	The median follow-up was 12.55 years. Using a nadir plus 2 ng/dL definition, Kaplan-Meier analysis demonstrated a biochemical DFS rate at 10 years of 80.56%, 74.16%, and 45.54% for low, moderate, and high-risk groups, respectively. The 10-year negative biopsy rate was 76.96%.	2
63. Merrick GS, Wallner KE, Butler WM. Prostate cryotherapy: more questions than answers. *Urology.* 2005;66(1):9-15.	Review/Other-Tx	N/A	No abstract available.	No abstract available.	4
64. Uchida T, Shoji S, Nakano M, et al. Transrectal high-intensity focused ultrasound for the treatment of localized prostate cancer: eight-year experience. *Int J Urol.* 2009;16(11):881-886.	Observational-Tx	517 patients	To report on the long-term results of high-intensity focused ultrasound in the treatment of localized prostate cancer.	Median follow-up period for all patients was 24 months. Biochemical disease-free rate in all patients at 5 years was 72%. Biochemical disease-free rate in patients with stage T1c, T2a, T2b, T2c and T3 groups at 5 years were 74%, 79%, 72%, 24% and 33%, respectively (P<0.0001). Biochemical disease-free rate in patients in the low-, intermediate-, and high-risk groups at 5 years were 84%, 64% and 45%, respectively (P<0.0001). Biochemical disease-free rate in patients treated with or without NHT at 7 years were 73% and 53% (P<0.0001), respectively. Pretreatment PSA levels (HR 1.060; P<0.0001; 95% CI, 1.040–1.080), NHT (HR 2.252; P<0.0001; 95% CI, 1.530–3.315) and stage (P=0.0189) were demonstrated to be statistically significant variables.	2
65. Thuroff S, Chaussy C. Evolution and outcomes of 3 MHz high intensity focused ultrasound therapy for localized prostate cancer during 15 years. *J Urol.* 2013;190(2):702-710.	Observational-Tx	704 patients	To describe the long-term cancer control and morbidity of high intensity focused ultrasound with neoadjuvant transurethral resection of the prostate, the risk of metastatic induction by transurethral prostate resection, and the evolution of high intensity focused ultrasound application and technology with time.	Of 704 study patients 78.5% had intermediate or high risk disease. Mean follow-up was 5.3 years (range 1.3 to 14). Cancer specific survival was 99%, metastasis-free survival was 95%, and 10-year salvage treatment-free rates were 98% in low risk, 72% in intermediate risk and 68% in high risk patients. Prostate specific antigen nadir and GS predicted BF, and side effects were moderate. The high intensity focused ultrasound re-treatment rate has been 15% since 2005.	1

Locally Advanced, High-Risk Prostate Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
66. Ellis DS, Manny TB, Jr., Rewcastle JC. Cryoablation as primary treatment for localized prostate cancer followed by penile rehabilitation. *Urology.* 2007;69(2):306-310.	Observational-Tx	416 patients	To determine the medium term efficacy and morbidity of patients who underwent cryoablation as primary therapy for localized prostate cancer followed by a penile rehabilitation regimen.	A total of 416 consecutive patients were treated. The mean patient age was 69.4 years, mean PSA level was 8.7 ng/mL, median GS was 6, and median stage was T1c. The mean follow-up of the entire population was 20.4 +/- 14.7 months. Of those continent before treatment, 4.0% were incontinent at 6 months but only 2 (0.6%) used any absorbent pads. Kaplan-Meier analysis demonstrated progressive recovery of sexual function of preoperatively potent men, with 41.4% +/- 4.3% and 51.3% +/- 5.9% potent 1 and 4 years after treatment, respectively. No patients had rectal fistula. The actuarial probability of remaining biochemically disease free at 4 years was 79.6% +/- 2.4%, with a mean time to failure of 4.2 months. After therapy, 168 patients underwent biopsy; 17 had positive findings (10.1%). The positive biopsy rate for the entire population was 4.1% (17/416).	2
67. Jones CU, Hunt D, McGowan DG, et al. Radiotherapy and short-term androgen deprivation for localized prostate cancer. *N Engl J Med.* 2011;365(2):107-118.	Experimental-Tx	1,979 patients	To evaluate whether adding short-term ADT to RT would improve survival among patients with nonbulky localized prostate adenocarcinomas and an initial PSA level of 20ng/mL or less.	The median follow-up period was 9.1 years. The 10-year rate of OS was 62% among patients receiving RT plus short-term ADT (the combined-therapy group), as compared with 57% among patients receiving RT alone (HR for death with RT alone, 1.17; *P*=0.03). The addition of short-term ADT was associated with a decrease in the 10-year disease-specific mortality from 8% to 4% (HR for RT alone, 1.87; *P*=0.001). BF, DM, and the rate of positive findings on repeat prostate biopsy at 2 years were significantly improved with RT plus short-term ADT. Acute and late radiation-induced toxic effects were similar in the 2 groups. The incidence of grade 3 or higher hormone-related toxic effects was <5%. Reanalysis according to risk showed reductions in overall and disease-specific mortality primarily among intermediate-risk patients, with no significant reductions among low-risk patients.	1

Locally Advanced, High-Risk Prostate Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
68. Laverdiere J, Gomez JL, Cusan L, et al. Beneficial effect of combination hormonal therapy administered prior and following external beam radiation therapy in localized prostate cancer. *Int J Radiat Oncol Biol Phys.* 1997;37(2):247-252.	Experimental-Tx	120 patients	To investigate whether combined androgen blockade associated with RT for localized prostate cancer decreases at 12 and 24 months the rate of positive follow-up biopsies and serum PSA compared to RT alone.	92 and 68 patients underwent biopsies at 12 and 24 months, respectively, after the end of RT. While 62% of control patients at 12 months in Group 1 disclosed residual neoplasm, only 30% and 4% showed residual disease in groups 2 and 3, respectively (P=0.00005). When looking at 24 months, 65%, 28%, and 5% showed residual cancer for groups 1, 2, and 3, respectively (P=0.00001). The PSA measurements indicate also at 12 months a difference between the 3 groups (P<0.0001), except at 24 months, the difference between the group 2 and 3 is no longer significant.	1
69. Gleave ME, Goldenberg SL, Chin JL, et al. Randomized comparative study of 3 versus 8-month neoadjuvant hormonal therapy before radical prostatectomy: biochemical and pathological effects. *J Urol.* 2001;166(2):500-506; discussion 506-507.	Experimental-Tx	547 patients stratified for T stage, Gleason grade, and pretreatment PSA	Prospective phase III, open label randomized controlled multicenter trial to determine whether 8-month compared with 3-month NHT reduces PSA recurrence rates after RP. Interim analysis shows secondary end points, including differences in biochemistry, pathology and adverse events between the 2 groups.	Men in 8-month group noticed higher number of newly reported adverse events (4.5 vs 2.9, P<0.0001) and higher incidence of hot flushes than 3-month group (87% vs 72%, respectively, P<0.0001). Ongoing biochemical and pathological regression of prostate tumors occurs between 3 and 8 months of NHT, suggesting that the optimal duration of NHT is longer than 3 months. Longer follow-up is needed to determine whether longer therapy alters PSA recurrence rates.	1

Locally Advanced, High-Risk Prostate Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
70. Zelefsky MJ, Reuter VE, Fuks Z, Scardino P, Shippy A. Influence of local tumor control on distant metastases and cancer related mortality after external beam radiotherapy for prostate cancer. *J Urol.* 2008;179(4):1368-1373; discussion 1373.	Observational-Tx	339 patients	To report local control outcomes, as assessed by post-treatment biopsies in patients who underwent 3-D conformal RT for clinically localized prostate cancer and to report the influence of local tumor control on long-term DM and CSS outcomes.	Overall biopsy outcomes in these patients were positive in 32%, severe treatment effect in 21% and negative in 47%. A higher radiation dose in the intermediate and high risk subgroups was associated with a lower incidence of positive biopsy. Of patients at intermediate risk who received a dose of 75.6 or greater 24% had a positive biopsy compared to 42% who received 70.2 Gy or less (P=0.03). In the high risk group positive treatment biopsies were noted in 51% of patients who received 70.2 Gy or less, 33% of those who received 75.6 Gy and 15% of those who received 81 Gy or greater (70.2 or less vs 75.6 Gy P=0.07 and 75.6 vs 81 Gy or greater P=0.05). Short course NADT before 3-D conformal RT had a significant impact on the post-treatment biopsy outcome. Of patients who did not receive ADT, 42% had a positive biopsy compared to 16% who received ADT (P<0.0001). Patients with negative and severe treatment effect biopsies had similar 10-year prostate specific antigen relapse-free survival outcomes that were markedly different from outcomes in those with positive treatment biopsies. Multivariate analysis indicated that the strongest predictor of BF was post-treatment biopsy status (positive vs severe treatment effect or negative P<0.001), followed by pretreatment prostate specific antigen (P=0.05) and clinical T stage (P=0.09). Similarly multivariate analysis revealed that a positive post-treatment biopsy was one of the strongest predictors of distant metastasis and prostate cancer death in this cohort of patients.	2

Locally Advanced, High-Risk Prostate Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
71. Pardo Y, Guedea F, Aguilo F, et al. Quality-of-life impact of primary treatments for localized prostate cancer in patients without hormonal treatment. *J Clin Oncol.* 2010;28(31):4687-4696.	Observational-Tx	435 patients	To compare the QoL impact of the 3 most common primary treatments on patients who were not receiving adjuvant hormonal treatment.	Compared with the brachytherapy group, the prostatectomy group showed greater deterioration on urinary incontinence and sexual scores but better urinary irritative-obstructive results (-18.22, -13.19, and +6.38, respectively, at 3 years; $P<.001$). In patients with urinary irritative-obstructive symptoms at baseline, improvement was observed in 64% of those treated with nerve-sparing RP. Higher bowel worsening (-2.87, $P=.04$) was observed in the external RT group, with 20% of patients reporting bowel symptoms.	1
72. Sanda MG, Dunn RL, Michalski J, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med.* 2008;358(12):1250-1261.	Observational-Tx	1,201 patients and 625 spouses or partners	To identify determinants of health-related QoL after primary treatment of prostate cancer and to measure the effects of such determinants on satisfaction with the outcome of treatment in patients and their spouses or partners.	Adjuvant hormone therapy was associated with worse outcomes across multiple QoL domains among patients receiving brachytherapy or RT. Patients in the brachytherapy group reported having long-lasting urinary irritation, bowel and sexual symptoms, and transient problems with vitality or hormonal function. Adverse effects of prostatectomy on sexual function were mitigated by nerve-sparing procedures. After prostatectomy, urinary incontinence was observed, but urinary irritation and obstruction improved, particularly in patients with large prostates. No treatment-related deaths occurred; serious adverse events were rare. Treatment-related symptoms were exacerbated by obesity, a large prostate size, a high PSA score, and older age. Black patients reported lower satisfaction with the degree of overall treatment outcomes. Changes in QoL were significantly associated with the degree of outcome satisfaction among patients and their spouses or partners.	1

Locally Advanced, High-Risk Prostate Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
73. Ferrer M, Guedea F, Suarez JF, et al. Quality of life impact of treatments for localized prostate cancer: cohort study with a 5 year follow-up. *Radiother Oncol.* 2013;108(2):306-313.	Observational-Tx	704 participants	To assess long-term QoL impact of treatments in localized prostate cancer patients treated with RP, EBRT or brachytherapy.	Brachytherapy's QoL impact was restricted to the urinary domain, Generalized Estimating Equation models showed score changes at 5-years of -12.0 (95% CI = -15.0, -9.0) in incontinence and -5.3 (95% CI = -7.5, -3.1) in irritative-obstructive scales. Compared to brachytherapy, RP fared +3.3 (95% CI = +0.0, +6.5) points better in irritative-obstructive but -17.1 (95% CI = -22.7, -11.5) worse in incontinence. Sexual deterioration was observed in RP (-19.1; 95% CI = -25.1, -13.1) and external RT groups (-7.5; 95% CI = -12.5, -2.5).	1
74. Gay HA, Michalski JM, Hamstra DA, et al. Neoadjuvant androgen deprivation therapy leads to immediate impairment of vitality/hormonal and sexual quality of life: results of a multicenter prospective study. *Urology.* 2013;82(6):1363-1368.	Experimental-Tx	450 patients	To evaluate the immediate effects of NADT on health-related QoL among patients undergoing RT for newly diagnosed prostate cancer.	From among 450 patients who completed the Expanded Prostate Cancer Index Composite-26 before and 2 months after NADT start, 71 received NADT before proceeding with definitive RT. Patients receiving NADT experienced significant impairment in vitality/hormonal (P<.0001) and sexual (P<.0001) health-related QoL after NADT initiation. The mean +/- standard deviation vitality/hormonal score fell from an average of 94.1 +/- 9.7 before NADT to 78.7 +/- 16.3 2 months after NADT initiation; and sexual health-related QoL fell from a mean of 51.7 +/- 31.1 pretreatment to 32.3 +/- 26.1 after NADT initiation. Both these health-related QoL domain changes exceeded the thresholds for clinical significance. Patients receiving NADT also experienced a significant impairment in urinary continence (P=.024), although this difference did not meet the criteria for clinical significance.	1

Locally Advanced, High-Risk Prostate Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
75. Hamstra DA, Conlon AS, Daignault S, et al. Multi-institutional prospective evaluation of bowel quality of life after prostate external beam radiation therapy identifies patient and treatment factors associated with patient-reported outcomes: the PROSTQA experience. *Int J Radiat Oncol Biol Phys.* 2013;86(3):546-553.	Observational-Tx	292 men	To evaluate patients treated with EBRT as part of the multicenter Prostate Cancer Outcomes and Satisfaction with Treatment Quality Assessment (PROSTQA), to identify factors associated with post-treatment patient-reported bowel health-related QoL.	Bowel health-related QoL had a median score of 100 (IQR 91.7–100) pretreatment and 95.8 (IQR 83.3–100) at 2 years, representing new moderate/big problems in 11% for urgency, 7% for frequency, 4% for bloody stools, and 8% for an overall bowel problems. Baseline bowel score was the strongest predictor for all 2-year endpoints. In multivariable models, a volume of rectum ≥25% treated to 70 Gy (V70) yielded a clinically significant 9.3-point lower bowel score (95% CI, 16.8–1.7, *P*=.015) and predicted increased risks for moderate to big fecal incontinence (*P*=.0008). No other RT treatment-related variables influenced moderate to big changes in rectal health-related QoL. However, on multivariate analyses V70 ≥25% was associated with increases in small, moderate, or big problems with the following: incontinence (3.9-fold; 95% CI, 1.1–13.4, *P*=.03), rectal bleeding (3.6-fold; 95% CI, 1.3–10.2, *P*=.018), and bowel urgency (2.9-fold; 95% CI, 1.1–7.6, *P*=.026). Aspirin use correlated with a clinically significant 4.7-point lower bowel summary score (95% CI, 9.0–0.4, *P*=.03) and an increase in small, moderate, or big problems with bloody stools (2.8-fold; 95% CI, 1.2–6.4, *P*=.018). IMRT was associated with higher RT doses to the prostate and lower doses to the rectum but did not independently correlate with bowel health-related QoL.	1

Locally Advanced, High-Risk Prostate Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
76. Resnick MJ, Koyama T, Fan KH, et al. Long-term functional outcomes after treatment for localized prostate cancer. *N Engl J Med.* 2013;368(5):436-445.	Observational-Tx	3,533 men	To compare long-term urinary, bowel, and sexual function after RP or EBRT.	Patients undergoing prostatectomy were more likely to have urinary incontinence than were those undergoing RT at 2 years (odds ratio, 6.22; 95% CI, 1.92 to 20.29) and 5 years (odds ratio, 5.10; 95% CI, 2.29 to 11.36). However, no significant between-group difference in the odds of urinary incontinence was noted at 15 years. Similarly, although patients undergoing prostatectomy were more likely to have erectile dysfunction at 2 years (odds ratio, 3.46; 95% CI, 1.93 to 6.17) and 5 years (odds ratio, 1.96; 95% CI, 1.05 to 3.63), no significant between-group difference was noted at 15 years. Patients undergoing prostatectomy were less likely to have bowel urgency at 2 years (odds ratio, 0.39; 95% CI, 0.22 to 0.68) and 5 years (odds ratio, 0.47; 95% CI, 0.26 to 0.84), again with no significant between-group difference in the odds of bowel urgency at 15 years.	2

Locally Advanced, High-Risk Prostate Cancer
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
77. Nguyen PL, Je Y, Schutz FA, et al. Association of androgen deprivation therapy with cardiovascular death in patients with prostate cancer: a meta-analysis of randomized trials. *JAMA.* 2011;306(21):2359-2366.	Meta-analysis	4,141 patients	To perform a systematic review and meta-analysis of randomized trials to determine whether ADT is associated with cardiovascular mortality, PCSM, and all-cause mortality in men with unfavorable-risk, nonmetastatic prostate cancer.	Among 4,141 patients from 8 randomized trials, cardiovascular death in patients receiving ADT vs control was not significantly different (255/2200 vs 252/1941 events; incidence, 11.0%; 95% CI, 8.3%–14.5%; vs 11.2%; 95% CI, 8.3%–15.0%; RR, 0.93; 95% CI, 0.79–1.10; *P*=.41). ADT was not associated with excess cardiovascular death in trials of at least 3 years (long duration) of ADT (11.5%; 95% CI, 8.1%–16.0%; vs 11.5%; 95% CI, 7.5%–17.3%; RR, 0.91; 95% CI, 0.75–1.10; *P*=.34) or in trials of 6 months or less (short duration) of ADT (10.5%; 95% CI, 6.3%–17.0%; vs 10.3%; 95% CI, 8.2%–13.0%; RR, 1.00; 95% CI, 0.73–1.37; *P*=.99). Among 4805 patients from 11 trials with overall death data, ADT was associated with lower PCSM (443/2527 vs 552/2278 events; 13.5%; 95% CI, 8.8%–20.3%; vs 22.1%; 95% CI, 15.1%–31.1%; RR, 0.69; 95% CI, 0.56–0.84; *P*<.001) and lower all-cause mortality (1140/2527 vs 1213/2278 events; 37.7%; 95% CI, 27.3%–49.4%; vs 44.4%; 95% CI, 32.5%–57.0%; RR, 0.86; 95% CI, 0.80–0.93; *P*<.001).	M
78. Levine GN, D'Amico AV, Berger P, et al. Androgen-deprivation therapy in prostate cancer and cardiovascular risk: a science advisory from the American Heart Association, American Cancer Society, and American Urological Association: endorsed by the American Society for Radiation Oncology. *Circulation.* 2010;121(6):833-840.	Review/Other-Tx	N/A	Advisory to review and summarize the metabolic effects of ADT, to evaluate the data regarding a possible relationship between ADT and cardiovascular events in patients with prostate cancer, and to generate suggestions regarding the evaluation and management of patients, both with and without known cardiac disease, in whom ADT is being initiated.	There is substantial amount of data demonstrating that ADT adversely affects traditional cardiovascular risk factors, including serum lipoproteins, insulin sensitivity, and obesity. Given the metabolic effects of ADT, it is advisable that patients in whom ADT is initiated be referred to their primary care physician for periodic follow-up evaluation.	4

Locally Advanced, High-Risk Prostate Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
79. Saylor PJ, Smith MR. Metabolic complications of androgen deprivation therapy for prostate cancer. *J Urol.* 2013;189(1 Suppl):S34-42; discussion S43-34.	Review/Other-Tx	N/A	A review focused on the more recently described metabolic complications of ADT including obesity, insulin resistance and lipid alterations as well as the association of ADT with diabetes and cardiovascular disease.	ADT decreases lean mass and increases fat mass. It also decreases insulin sensitivity while increasing low density lipoprotein cholesterol, high density lipoprotein cholesterol and triglycerides. Consistent with these adverse metabolic effects, ADT may be associated with a greater incidence of diabetes and cardiovascular disease. Some of these ADT related metabolic changes (obesity, insulin resistance and increased triglycerides) overlap with features of the metabolic syndrome. However, in contrast to the metabolic syndrome, ADT increases subcutaneous fat and high density lipoprotein cholesterol.	4

Evidence Table Key

Study Quality Category Definitions

- *Category 1* The study is well-designed and accounts for common biases.
- *Category 2* The study is moderately well-designed and accounts for most common biases.
- *Category 3* There are important study design limitations.
- *Category 4* The study is not useful as primary evidence. The article may not be a clinical study or the study design is invalid, or conclusions are based on expert consensus. For example:
  a) the study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description);
  b) the study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence;
  c) the study is an expert opinion or consensus document.
- M = Meta-analysis

Dx = Diagnostic

Tx = Treatment

Abbreviations Key

ADT = Androgen deprivation therapy
ART = Adjuvant radiation therapy
AST = Androgen-suppression therapy
BF = Biochemical failure
bPFS = Biochemical progression-free survival
CI = Confidence interval
CSS = Cause-specific survival
DFS = Disease-free survival
DM = Distant metastases
EBRT = External beam radiation therapy
FFbF = Freedom from biochemical failure
FFM = Freedom from metastasis
GS = Gleason score
HR = Hazard ratio
HT = Hormonal therapy
IMRT = Intensity modulated radiation therapy
MRI = Magnetic resonance imaging
NADT = Neoadjuvant androgen deprivation therapy
NHT = Neoadjuvant hormonal therapy
IQR = Interquartile range
OS = Overall survival
PCSM = Prostate cancer-specific mortality
PNI = Perineural invasion
PSA = Prostate-specific antigen
QoL = Quality-of-life
RP = Radical prostatectomy
RT = Radiation therapy
WPRT = Whole pelvic radiotherapy