Definitive External Beam Irradiation in Stage T1 and T2 Prostate Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. Hanks GE, Hanlon AL, Schultheiss TE, et al. Conformal external beam treatment of prostate cancer. *Urology* 1997; 50(1):87-92.	Observational-Tx	456 consecutive patients	A report on 5-year outcomes of treatment for patients with prostate cancer treated largely with 3D-CRT.	5-year bNED rate for all patients was 61% and 57% at 7 years. In the group with pretreatment PSA <10 ng/mL, the 5-year bNED rate for patients with localized disease (T1, 2AB disease, Gleason sum of ≤6) was 85% and for those with locally advanced disease (T2C, 3), 70%. In the group with pretreatment PSA of 10-19.9 ng/mL, the 5-year bNED rate for patients with localized disease was 66% and for those with locally advanced disease, 44%. In the group with pretreatment PSA of 20 ng/mL or above, the patients with localized or locally advanced disease had 5-year bNED rates of 31% and 21%, respectively.	2
2. Perez CA, Cosmatos D, Garcia DM, Eisbruch A, Poulter CA. Irradiation in relapsing carcinoma of the prostate. *Cancer* 1993; 71(3 Suppl):1110-1122.	Review/Other-Tx	N/A	To review techniques and results reported for various indications of RT.	23 patients with isolated postprostatectomy local recurrences treated with doses of 60-65 Gy, 17 (74%) had tumor control, and 45% survived relapse-free for 5 years after treatment of the recurrence. Significant improvement of neurologic function has been reported in 36%-60% of the patients, depending on severity of deficit and promptness in instituting emergency treatment.	4
3. Potters L, Klein EA, Kattan MW, et al. Monotherapy for stage T1-T2 prostate cancer: radical prostatectomy, external beam radiotherapy, or permanent seed implantation. *Radiother Oncol* 2004; 71(1):29-33.	Observational-Tx	1,819 consecutively treated clinical stage T1-T2: RT for 340, RP for 746, and PPB for 733 cases	To review the freedom from biochemical recurrence rates after PPB, EBRT to a minimum 70 Gy, or RP for clinically localized stage T1-T2 adenocarcinoma of the prostate.	The 7-year freedom from biochemical recurrence rates for PPB vs EBRT vs RP were 74%, 77%, and 79%, respectively. PSA levels and pretreatment GS were the best predictor of outcome. Once these were controlled for, there was no difference in outcome for any of the monotherapy.	2
4. Vicini FA, Martinez A, Hanks G, et al. An interinstitutional and interspecialty comparison of treatment outcome data for patients with prostate carcinoma based on predefined prognostic categories and minimum follow-up. *Cancer* 2002; 95(10):2126-2135.	Observational-Tx	6,877 men with prostate cancer	An observational retrospective study. To compare outcomes for patients with localized disease treated differently at different institutions.	Prognostic factors accounted for much of the variation seen and once these were accounted for there was remarkable similarity in outcomes across therapeutic modality and across institution. However, clinical trials will be needed for definitive results on efficacy.	2

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5. 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.	2

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6. Bill-Axelson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med* 2011; 364(18):1708-1717.	Experimental-Tx	695 men	To report 15-year results of RP compared with watchful waiting in early prostate cancer.	During a median of 12.8 years, 166/347 men in the radical-prostatectomy group and 201/348 in the watchful-waiting group died (P=0.007). In the case of 55 men assigned to surgery and 81 men assigned to watchful waiting, death was due to prostate cancer. This yielded a cumulative incidence of death from prostate cancer at 15 years of 14.6% and 20.7%, respectively (a difference of 6.1 percentage points; 95% CI, 0.2 to 12.0), and a RR with surgery of 0.62 (95% CI, 0.44 to 0.87; P=0.01). The survival benefit was similar before and after 9 years of follow-up, was observed also among men with low-risk prostate cancer, and was confined to men <65 years of age. The number needed to treat to avert one death was 15 overall and 7 for men <65 years of age. Among men who underwent RP, those with extracapsular tumor growth had a risk of death from prostate cancer that was 7 times that of men without extracapsular tumor growth (RR, 6.9; 95% CI, 2.6 to 18.4).	1

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7. Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med* 2012; 367(3):203-213.	Experimental-Tx	731 men	To compare the effectiveness of surgery with observation for men with localized prostate cancer detected by means of PSA testing.	During the median follow-up of 10.0 years, 171/364 men (47.0%) assigned to RP died, as compared with 183/367 (49.9%) assigned to observation (HR, 0.88; 95% CI, 0.71 to 1.08; P=0.22; absolute risk reduction, 2.9 percentage points). Among men assigned to RP, 21 (5.8%) died from prostate cancer or treatment, as compared with 31 men (8.4%) assigned to observation (HR, 0.63; 95% CI, 0.36 to 1.09; P=0.09; absolute risk reduction, 2.6 percentage points). The effect of treatment on all-cause and prostate-cancer mortality did not differ according to age, race, coexisting conditions, self-reported performance status, or histologic features of the tumor. RP was associated with reduced all-cause mortality among men with a PSA value >10 ng/mL (P=0.04 for interaction) and possibly among those with intermediate-risk or high-risk tumors (P=0.07 for interaction). Adverse events within 30 days after surgery occurred in 21.4% of men, including one death.	1

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8. Widmark A, Tomic R, Modig C, et al. Prospective randomized trial comparing external beam radiotherapy versus watchful waiting in early prostate cancer (T1b-T2, pN0, grade 1–2, M0). Presented at the 53rd Annual ASTRO Meeting; Miami Beach, FL. October 2–6, 2011; abstract. 2011.	Experimental-Tx	214 patients	Prospective randomized trial comparing EBRT vs watchful waiting in early prostate cancer.	This analysis is based on 138 deaths. With a minimum follow-up of 16 years, 74 patients (69%) in the watchful waiting group and 64 (60%) in the EBRT group have died, giving a 20 years OS of 0.31 (0.22-0.42) and 0.35 (0.25-0.48) respectively (P for difference=0.26). The numbers for prostate cancer specific deaths after 15 years was 25 (23%) and 19 (18%), respectively giving a prostate cancer-specific survival of 0.72 (0.63-0.83) and 0.79 (0.71-0.89), respectively (P for difference=0.31). Distant progression was observed in 33/107; 31% in the watchful waiting group and 18/107; 17% in the EBRT group, resulting in a 15 year recurrence free survival of 0.66 (0.57-0.77) and 0.81 (0.74-0.90), respectively, (P for difference=0.022). Clinical progression (Biochemical + Local), that made the treating doctor change the treatment of the patient, was 58% in the watchful waiting arm and 29% in the EBRT arm, giving a 15 years recurrence free survival of 0.40 (0.31-0.51) and 0.67 (0.58-0.78), respectively, (P for difference<0,0001). Biochemical and local progression were both significantly in favor of EBRT.	1
9. Hayes JH, Ollendorf DA, Pearson SD, et al. Active surveillance compared with initial treatment for men with low-risk prostate cancer: a decision analysis. *JAMA* 2010; 304(21):2373-2380.	Review/Other-Tx	Hypothetical cohorts of 65-year-old men	To examine the QoL benefits and risks of active surveillance compared with initial treatment for men with low-risk, clinically localized prostate cancer.	Active surveillance was associated with the greatest QALE (11.07 QALYs), followed by brachytherapy (10.57 QALYs), IMRT (10.51 QALYs), and RP (10.23 QALYs). Active surveillance remained associated with the highest QALE even if the RR of prostate cancer-specific death for initial treatment vs active surveillance was as low as 0.6. However, the QALE gains and the optimal strategy were highly dependent on individual preferences for living under active surveillance and for having been treated.	4

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10. Klotz L, Zhang L, Lam A, Nam R, Mamedov A, Loblaw A. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. *J Clin Oncol* 2010; 28(1):126-131.	Observational-Tx	450 patients	Prospective cohort study to assess the outcome of a watchful-waiting protocol with selective delayed intervention by using clinical PSA, or histologic progression as treatment indications for clinically localized prostate cancer.	Median follow-up was 6.8 years (range, 1 to 13 years). OS was 78.6%. The 10-year prostate cancer actuarial survival was 97.2%. Overall, 30% of patients have been reclassified as higher risk and have been offered definitive therapy. Of 117 patients treated radically, the PSA failure rate was 50%, which was 13% of the total cohort. PSA doubling time of 3 years or less was associated with an 8.5-times higher risk of biochemical failure after definitive treatment compared with a doubling time of more than 3 years (P<.0001). The HR for nonprostate cancer to prostate cancer mortality was 18.6 at 10 years.	2
11. Tosoian JJ, Trock BJ, Landis P, et al. Active surveillance program for prostate cancer: an update of the Johns Hopkins experience. *J Clin Oncol* 2011; 29(16):2185-2190.	Observational-Tx	769 men	To assess outcomes of men with prostate cancer enrolled in active surveillance.	The median survival free of intervention was 6.5 years (range, 0.0 to 15.0 years) after diagnosis, and the proportions of men remaining free of intervention after 2, 5, and 10 years of follow-up were 81%, 59%, and 41%, respectively. Overall, 255 men (33.2%) underwent intervention at a median of 2.2 years (range, 0.6 to 10.2 years) after diagnosis; 188 men (73.7%) underwent intervention on the basis of disease reclassification on biopsy. The proportions of men who underwent curative intervention (P=.026) or had biopsy reclassification (P<.001) were significantly lower in men who met enrollment criteria than in those who did not. There were no prostate cancer deaths.	2

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12. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998; 280(11):969-974.	Observational-Tx	1,872 patients: 888 treated with RP; 218 treated with implant with or without neoadjuvant ADT; 766 treated with RT	To estimate control of PSA after RP, EBRT, or implant with or without neoadjuvant ADT in patients with clinically localized prostate cancer.	The RR of PSA failure in low-risk patients (stage T1c, T2a and PSA level ≤10 ng/mL and GS ≤6) treated using RT, implant plus ADT, or implant therapy was 1.1 compared with those patients treated with RP. The addition of ADT to implant therapy did not improve PSA outcome in high-risk patients but resulted in a PSA outcome that was not statistically different compared with the results obtained using RP or RT in intermediate-risk patients. Intermediate- and high-risk patients treated with EBRT or RP fared better than brachytherapy.	2
13. Mohler JL, Armstrong AJ, Bahnson RR, et al. Prostate Cancer, Version 3.2012 Featured Updates to the NCCN Guidelines. *J Natl Compr Canc Netw* 2012; 10(9):1081-1087.	Review/Other-Tx	N/A	Featured updated to the NCCN Guidelines.	Abiraterone acetate is a first-in-class hormonal agent that represents a new standard of care for patients with metastatic castration-recurrent prostate cancer who have previously received docetaxel (category 1 recommendation). Abiraterone acetate also received category 2B recommendations in the prechemotherapy setting for asymptomatic patients or symptomatic patients who are not candidates for docetaxel. The NCCN Prostate Cancer Panel also added new indications for existing agents, including the option of sipuleucel-T as second-line therapy. In addition, brachytherapy in combination with EBRT with or without ADT is now an alternative for patients with high-risk localized tumors or locally advanced disease.	4
14. D'Amico AV, Schultz D, Silver B, et al. The clinical utility of the percent of positive prostate biopsies in predicting biochemical outcome following external-beam radiation therapy for patients with clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2001; 49(3):679-684.	Observational-Tx	473 men	To determine if percent of positive biopsies was a good predictor of PSA levels for patients treated with EBRT.	Controlling for the known prognostic factors, the percent of positive prostate biopsies added clinically significant information (P=0.02) regarding time to PSA failure following RT. Specifically, 76% of the patients in the intermediate risk group (1992 AJCC T(2b) or biopsy Gleason 7 or PSA >10 ng/mL and ≤20 ng/mL) could be classified into either an 30% or 85% 5-year PSA control cohort using the preoperative prostate biopsy data.	2

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15. D'Amico AV, Chen MH, Roehl KA, Catalona WJ. Preoperative PSA velocity and the risk of death from prostate cancer after radical prostatectomy. *N Engl J Med* 2004; 351(2):125-135.	Observational-Tx	1,095 men	To determine whether men at risk for death from prostate cancer after RP can be identified using information available at diagnosis.	As compared with an annual PSA velocity of ≤2.0 ng/mL, an annual PSA velocity of >2.0 ng/mL was associated with a significantly shorter time to death from prostate cancer (P<0.001) and death from any cause (P=0.01). An increasing PSA level at diagnosis (P=0.01), a GS of 8, 9, or 10 (P=0.02), and a clinical tumor stage of T2 (P<0.001) also predicted the time to death from prostate cancer. For men with an annual PSA velocity of >2.0 ng/mL, estimates of the risk of death from prostate cancer and death from any cause 7 years after RP were also influenced by the PSA level, tumor stage, and GS at diagnosis.	2
16. D'Amico AV, Renshaw AA, Sussman B, Chen MH. Pretreatment PSA velocity and risk of death from prostate cancer following external beam radiation therapy. *JAMA* 2005; 294(4):440-447.	Observational-Tx	358 men	To assess whether a >2.0-ng/mL increase in PSA level during the year prior to diagnosis was significantly associated with prostate cancer-specific mortality following RT.	A PSA velocity >2.0 ng/mL per year was significantly associated with a shorter time to prostate cancer-specific mortality (adjusted HR, 12.0; 95% CI, 3.0-54.0; P=.001) and all-cause mortality (adjusted HR, 2.1; 95% CI, 1.3-3.6; P=.005) when compared with men whose PSA velocity was ≤2.0 ng/mL per year. Men presenting with low-risk disease and a PSA velocity >2.0 ng/mL per year had a 7-year estimate of prostate cancer-specific mortality of 19% (95% CI, 2%-39%) compared with 0% for men whose PSA velocity was ≤2.0 ng/mL per years. The corresponding values for men with higher-risk disease were 24% (95% CI, 12%-37%) and 4% (95% CI, 0%-11%), respectively.	2
17. Patel AA, Chen MH, Renshaw AA, D'Amico AV. PSA failure following definitive treatment of prostate cancer having biopsy Gleason score 7 with tertiary grade 5. *JAMA* 2007; 298(13):1533-1538.	Observational-Tx	2,370 men	To compare the prognostic significance of GS 7 with tertiary grade 5 vs other GSs with respect to time to PSA failure in men with prostate cancer.	Men with GS 7 and tertiary grade 5 disease had a significantly shorter time to PSA failure than men with 7 without tertiary grade 5 (median time, 5.0 vs 6.7 years, respectively; adjusted HR, 0.56; 95% CI, 0.32-0.97; P=.04) or score of 6 or less (median time, 15.4 years; adjusted HR, 0.24; 95% CI, 0.13-0.43; P<.001). However, a significant difference was not observed when these men were compared with men with GS 8 to 10 disease (median time, 5.1 years; adjusted HR, 0.96; 95% CI, 0.54-1.71; P=.90).	2

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18. 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 GI toxicity (rectal bleeding grade >3, three patients (0·5%) in the ADT only group, two (0·3%) in the ADT and RT group; diarrhea grade >3, four patients (0·7%) vs eight (1·3%); urinary toxicity grade >3, 14 patients (2·3%) in both groups).	1
19. 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 prostate-cancer-specific mortality 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 RR 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 RR 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
20. 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, freedom from biochemical 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

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21. Zietman AL, Bae K, Slater JD, et al. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/american college of radiology 95-09. *J Clin Oncol* 2010; 28(7):1106-1111.	Experimental-Tx	393 men	Randomized study to determine whether increasing radiation dose delivered to men with early-stage prostate cancer improves clinical outcomes.	Median follow-up was 8.9 years. Men receiving high-dose RT were significantly less likely to have local failure, with a HR of 0.57. The 10-year ASTRO biochemical free rates were 32.4% for conventional-dose and 16.7% for high-dose RT (P<.0001). Trial shows superior long-term cancer control for men with localized prostate cancer receiving high-dose vs conventional-dose radiation. This was achieved without an increase in grade ≥3 late urinary or rectal morbidity.	1
22. Zietman AL, DeSilvio ML, Slater JD, et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. *JAMA* 2005; 294(10):1233-1239.	Experimental-Tx	393 patients	Randomized trial to determine whether increasing the radiation dose delivered to men with clinically localized prostate cancer improves disease outcome.	The proportions of men free from biochemical failure at 5 years were 78.8% [corrected] (95% CI, 73.1%-84.6%) [corrected] for conventional-dose and 91.3% [corrected] (95% CI, 87.2%-95.4%) [corrected] for high-dose therapy (P<.001), a 59% [corrected] reduction in the risk of failure. Men with clinically localized prostate cancer have a lower risk of biochemical failure if they receive high-dose rather than conventional-dose conformal radiation.	1
23. Roach M, 3rd, DeSilvio M, Lawton C, et al. Phase III trial comparing whole-pelvic versus prostate-only radiotherapy and neoadjuvant versus adjuvant combined androgen suppression: Radiation Therapy Oncology Group 9413. *J Clin Oncol* 2003; 21(10):1904-1911.	Experimental-Tx	1,292 patients	To test the hypothesis that combined androgen suppression and WPRT followed by a boost to the prostate improves PFS by 10% compared with combined androgen suppression and prostate-only RT. This trial also tested the hypothesis that NCHT improves PFS compared with AHT by 10%.	WPRT was associated with a 4-year PFS of 54% compared with 47% in patients treated with prostate-only RT (P=.022). Patients treated with NCHT experienced a 4-year PFS of 52% vs 49% for AHT (P=.56). When comparing all four arms, there was a progression-free difference among WPRT + NCHT, prostate-only RT + NCHT, WPRT + AHT, and prostate-only RT + AHT (60% vs 44% vs 49% vs 50%, respectively; P=.008). No survival advantage has yet been seen./ WPRT + NCHT improves PFS compared with prostate-only RT and NCHT or prostate-only RT and AHT, and compared with WPRT + AHT in patients with a risk of LN involvement of 15%.	1

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24. 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 AHT by ≥10%.	The difference in OS for the four arms was statistically significant (P=0.027). However, no statistically significant differences were found in PFS or OS between NHT vs AHT 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 + AHT arms.	1
25. 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 two treatment arms for the whole series and for each stratified group. On multivariate analysis, low LNI risk and hormonal therapy 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
26. Roach M, 3rd. Targeting pelvic lymph nodes in men with intermediate- and high-risk prostate cancer, and confusion about the results of the randomized trials. *J Clin Oncol* 2008; 26(22):3816-3817; author reply 3817-3818.	Review/Other-Tx	N/A	Letter to editor criticizing a study by Nguyen PL and D'Amico AV: titled "Targeting pelvic lymph nodes in men with intermediate- and high-risk prostate cancer despite two negative randomized trials."	According to Roach M, the assumptions and conclusions in the study by Nguyen PL and D'Amico AV about WPRT are wrong.	4
27. Wang-Chesebro A, Xia P, Coleman J, Akazawa C, Roach M, 3rd. Intensity-modulated radiotherapy improves lymph node coverage and dose to critical structures compared with three-dimensional conformal radiation therapy in clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2006; 66(3):654-662.	Observational-Tx	35 patients	To quantify gains in lymph node coverage and critical structure dose reduction for WPRT and EFRT in prostate cancer using IMRT compared with 3D-CRT for the first treatment phase of 45 Gy in the concurrent treatment of lymph nodes and prostate.	For Group 1, WPRT 3D-CRT missed 25% of pelvic nodes with the prescribed dose 45 Gy and missed 18% with the 95% prescribed dose 42.75 Gy, whereas WPRT IMRT achieved V(45 Gy) = 98% and V(42.75 Gy) = 100%. Compared with WPRT 3D-CRT, IMRT reduced bladder V(45 Gy) by 78%, rectum V(45 Gy) by 48%, and small bowel V(45 Gy) by 232 cm3. EFRT 3D-CRT achieved 95% coverage of nodes for all patients at high cost to critical structures. For Group 2, IMRT decreased bladder V(45 Gy) by 90%, rectum V(45 Gy) by 54% and small bowel V(45 Gy) by 455 cm3 compared with EFRT 3D-CRT.	2

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28. Chan LW, Xia P, Gottschalk AR, et al. Proposed rectal dose constraints for patients undergoing definitive whole pelvic radiotherapy for clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008; 72(1):69-77.	Review/Other-Tx	8 studies	The purpose of this study was to develop a set of standardized, literature-based constraints for patients undergoing WPRT for prostate cancer, demonstrate that they are achievable, and assess the corresponding rectal toxicity.	A continuous, proposed rectal dose-constraint curve was generated. IMRT not only met this constraint curve, but also was able to achieve at least 30%-40% lower dose to the rectum. The preliminary clinical results were also positive: 50% of patients reported no acute bowel toxicity, 33% reported Grade 1 toxicity, and 17% reported Grade 2 toxicity. No patients reported Grade 3-4 acute rectal toxicity.	4
29. Sylvester JE, Grimm PD, Blasko JC, et al. 15-Year biochemical relapse free survival in clinical Stage T1-T3 prostate cancer following combined external beam radiotherapy and brachytherapy; Seattle experience. *Int J Radiat Oncol Biol Phys* 2007; 67(1):57-64.	Observational-Tx	223 patients	To report the Seattle 15-year results of transperineal interstitial PPB combined with moderate-dose neoadjuvant EBRT in a group of consecutively treated and prospectively followed patients with clinical T1-T3 prostate cancer.	15-year bRFS for the entire treatment group was 74%. bRFS using the Memorial Sloan-Kettering risk cohort analysis (95% CI): low risk, 88%, intermediate risk 80%, and high risk 53%. Grouping by the risk classification described by D'Amico, the bRFS was: low risk 85.8%, intermediate risk 80.3%, and high risk 67.8% (P=0.002).	1
30. Lettmaier S, Lotter M, Kreppner S, Strnad A, Fietkau R, Strnad V. Long term results of a prospective dose escalation phase-II trial: interstitial pulsed-dose-rate brachytherapy as boost for intermediate- and high-risk prostate cancer. *Radiother Oncol* 2012; 104(2):181-186.	Observational-Tx	130 patients	To review a 7 year single institution experience with pulsed dose rate brachytherapy dose escalation study in patients with intermediate and high risk prostate cancer.	At the time of analysis with a median follow-up of 60 months biochemical control was achieved by 88% of patients; only 16/130 patients (12.3%) developed a biochemical relapse. bRFS calculated according to Kaplan-Meier for all patients at 5 years was 85.6% (83.9% for intermediate-risk patients and 84.2% for high-risk patients) and at 9 years' follow-up it was 79.0%. Analyzing bRFS separately for different boost dose levels, at 5 years it was 97% for the 35 Gy boost dose and 82% for the 25 and 30 Gy dose levels. The side effects of therapy were negligible: There were 18 cases (15%) of grade 1/2 rectal proctitis, one case (0.8%) of grade 3 proctitis, 18 cases (15%) of grade 1/2 cystitis, and no cases (0%) with dysuria grade 3. No patient had a bulbourethral stricture requiring dilation or new onset incontinence.	1

Definitive External Beam Irradiation in Stage T1 and T2 Prostate Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
31. Hurwitz MD, Halabi S, Archer L, et al. Combination external beam radiation and brachytherapy boost with androgen deprivation for treatment of intermediate-risk prostate cancer: long-term results of CALGB 99809. *Cancer* 2011; 117(24):5579-5588.	Observational-Tx	61 patients	To present long-term efficacy and toxicity results of a multicenter phase 2 trial assessing combination of EBRT and transperineal prostate brachytherapy boost with ADT for intermediate-risk prostate cancer.	61/63 enrolled patients were eligible. Median follow-up was 73 months. Late grade 2 and 3 toxicity, excluding sexual dysfunction, occurred in 20% and 3% of patients. 6-year DFS applying the protocol definition, 1997 ASTRO consensus, and Phoenix definitions was 87.1%, 75.1%, and 84.9%. 6 deaths occurred; only 1 was attributed to prostate cancer. 6-year OS was 96.1%.	2
32. Hoskin PJ, Rojas AM, Bownes PJ, Lowe GJ, Ostler PJ, Bryant L. Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer. *Radiother Oncol* 2012; 103(2):217-222.	Experimental-Tx	218 patients	A prospective randomized trial to compare EBRT alone with a combined schedule including a high-dose-rate brachytherapy boost and to present survival data and urinary and bowel late adverse events up to 10 years after treatment.	Relapse free survival was significantly higher in patients treated with EBRT+ high-dose-rate brachytherapy (log rank P=0.04). In multivariate analysis treatment arm, risk category and ADT were significant covariates for risk of relapse. Differences in OS were not significant. Incidence of severe late urinary and bowel morbidity was similar.	1
33. Sathya JR, Davis IR, Julian JA, et al. Randomized trial comparing iridium implant plus external-beam radiation therapy with external-beam radiation therapy alone in node-negative locally advanced cancer of the prostate. *J Clin Oncol* 2005; 23(6):1192-1199.	Experimental-Tx	51 patients received IMRT plus EBRT, and 53 patients received EBRT alone	To determine if iridium implant (IM) and EBRT is better than standard EBRT in locally advanced prostate cancer.	Between 1992 and 1997, 51 patients were randomly assigned to receive iridium implant plus EBRT, and 53 patients were randomly assigned to receive EBRT alone. The median follow-up was 8.2 years. In the iridium implant plus EBRT arm, 17 patients (29%) experienced biochemical failure compared with 33 patients (61%) in the EBRT arm (HR, 0.42; P=.0024). 87 patients (84%) had a postradiation biopsy; 10 (24%) of 42 in the iridium implant plus EBRT arm had biopsy positivity compared with 23 (51%) of 45 in the EBRT arm (odds ratio, 0.30; P=.015). OS was 94% in the iridium implant plus EBRT arm vs 92% in the EBRT arm.	1

Definitive External Beam Irradiation in Stage T1 and T2 Prostate Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
34. 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	To report on a retrospective comparison of biochemical outcomes using an ultra-high dose of conventionally fractionated IMRT vs a lower dose of IMRT combined with high-dose-rate brachytherapy to increase the biologically effective dose of IMRT.	The 5-year actuarial PSA relapse-free survival for high-dose-rate plus IMRT vs ultra-high-dose IMRT were 100% vs 98%, 98% vs 84%, and 93% vs 71%, for National Comprehensive Cancer Network 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. High-dose-rate 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.	2
35. Zelefsky MJ, Leibel SA, Gaudin PB, et al. Dose escalation with three-dimensional conformal radiation therapy affects the outcome in prostate cancer. *Int J Radiat Oncol Biol Phys* 1998; 41(3):491-500.	Observational-Tx	743 patients	To determine whether dose escalation with 3D-CRT improves outcomes.	The median follow-up was 3 years (range: 1-7.6 years). Induction of an initial clinical response was dose-dependent, with 90% of patients receiving 75.6 or 81.0 Gy achieving a PSA nadir ≤1.0 ng compared with 76% and 56% for those treated with 70.2 Gy and 64.8 Gy, respectively (P<0.001). The 5-year actuarial PSA relapse-free survival for patients with favorable prognostic indicators (stage T1-2, pretreatment PSA ≤10.0 ng/ml and GS ≤6) was 85%, compared to 65% for those with intermediate prognosis (one of the prognostic indicators with a higher value) and 35% for the group with unfavorable prognosis (two or more indicators with higher values) (P<0.001). PSA relapse-free survival was significantly improved in patients with intermediate and unfavorable prognosis receiving ≥75.6 Gy (P<0.05). A positive biopsy at ≥2.5 years after 3D-CRT was observed in only 1/15 (7%) of patients receiving 81.0 Gy, compared with 12/25 (48%) after 75.6 Gy, 19/42 (45%) after 70.2 Gy, and 13/23 (57%) after 64.8 Gy (P<0.05).	2

Definitive External Beam Irradiation in Stage T1 and T2 Prostate Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
36. Zelefsky MJ, Fuks Z, Hunt M, et al. High-dose intensity modulated radiation therapy for prostate cancer: early toxicity and biochemical outcome in 772 patients. *Int J Radiat Oncol Biol Phys* 2002; 53(5):1111-1116.	Observational-Tx	772 patients	Report on the toxicity and biochemical outcomes for patients treated with IMRT.	4.5% had Grade 2 rectal toxicity (no Grade 3), 28% had Grade 2 urinary symptoms (1 with Grade 3). The 3 year relapse free survival was 92%, 86%, and 81%, respectively by risk group. This shows that IMRT can achieve good outcomes while reducing morbidity.	2
37. 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.	Observational-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 bRFS 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 distant metastases. No prostate cancer-related deaths were observed in the low-risk group. The 7-year prostate cancer-specific mortality 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 prostate cancer-specific mortality. Actuarial 7-year grade 2 or higher late GI and GU toxicities were 4.4% and 21.1%, respectively. Late grade 3 GI and GU 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

Definitive External Beam Irradiation in Stage T1 and T2 Prostate Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
38. Michalski JM, Yan Y, Watkins-Bruner D, et al. Preliminary Analysis of 3D-CRT vs. IMRT on the High Dose Arm of the RTOG 0126 Prostate Cancer Trial: Toxicity Report. *Int J Radiat Oncol Biol Phys* 2011; 81(2):S1-S2.	Observational-Tx	748 patients	Preliminary analysis of clinical and treatment characteristics associated with acute and late toxicity in men receiving high dose RT on a Phase III RTOG dose escalation trial.	Median follow-up was 4.6 years and 3.5 years for 3D-CRT and IMRT patients. Median D98 delivered to the planning target volume 7920 was 80 Gy for 3D-CRT and 79.2 Gy for IMRT. The median percentage of the bladder receiving at least x Gy, pVx, for pV65, pV70, and pV75 were 25.3%, 22.2%, and 17.7%, respectively, for 3D-CRT, and 19.7%, 16.6%, and 13.1%, respectively, for IMRT. The median rectum pV65, pV70, and pV75 were 27.4%, 21.7%, and 15.8% for 3D-CRT and 23.0%, 18.2%, and 13.0% for IMRT. For both bladder and rectum, the pVx was significantly lower with IMRT for 65, 70, and 75 Gy (all P=0.0001). Acute toxicity; there are 16.9% Grade (G2), 2.5% G3, and no G4 or 5 in the 3D-CRT group; there are 13.9% G2, 2.4% G3, 0.4% G4, and no G5 in the IMRT group. Late toxicity; there are 23.6% G2, 8.9% G3, 0.4% G4, and 0.2% G5 (1 death) with 3D-CRT group; there are 19.9% G2, 4.7% G3, 0.4% G4, and no G5 with IMRT. For G2+ acute GI/GU toxicity, both univariate and multivariate analyses show a statistically significant decrease in G2+ acute collective GI/GU toxicity for IMRT.	1
39. Chung HT, Xia P, Chan LW, Park-Somers E, Roach M, 3rd. Does image-guided radiotherapy improve toxicity profile in whole pelvic-treated high-risk prostate cancer? Comparison between IG-IMRT and IMRT. *Int J Radiat Oncol Biol Phys* 2009; 73(1):53-60.	Observational-Tx	25 consecutively treated patients	To evaluate the impact of adding IGRT to IMRT on dosimetric avoidance of organs at risk and acute toxicities.	The planning target volume dose coverage was not significantly different between IMRT and IGRT-IMRT for the prostate, seminal vesicles, and lymph nodes. The volume of rectum and bladder receiving ≥40, ≥60, and ≥70 Gy were all significantly less using IGRT-IMRT (P<.001). IGRT-IMRT yielded lower acute RTOG Grade 2 rectal (80% vs 13%, P= 0.004) and bladder (60% vs 13%, P= 0.014) toxicities.	2

Definitive External Beam Irradiation in Stage T1 and T2 Prostate Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
40. Zelefsky MJ, Kollmeier M, Cox B, et al. Improved clinical outcomes with high-dose image guided radiotherapy compared with non-IGRT for the treatment of clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2012; 84(1):125-129.	Observational-Tx	186 patients	To compare toxicity profiles and biochemical tumor control outcomes between patients treated with high-dose IGRT and high-dose IMRT for clinically localized prostate cancer.	A significant reduction in late urinary toxicity was observed for IGRT patients compared with the non-IGRT patients. The 3-year likelihood of grade 2 and higher urinary toxicity for the IGRT and non-IGRT cohorts were 10.4% and 20.0%, respectively (P=0.02). Multivariate analysis identifying predictors for grade 2 or higher late urinary toxicity demonstrated that, in addition to the baseline International Prostate Symptom Score, IGRT was associated with significantly less late urinary toxicity compared with non-IGRT. The incidence of grade 2 and higher rectal toxicity was low for both treatment groups (1.0% and 1.6%, respectively; P=0.81). No differences in PSA relapse-free survival outcomes were observed for low- and intermediate-risk patients when treated with IGRT and non-IGRT. For high-risk patients, a significant improvement was observed at 3 years for patients treated with IGRT compared with non-IGRT.	2
41. Konski A, Speier W, Hanlon A, Beck JR, Pollack A. Is proton beam therapy cost effective in the treatment of adenocarcinoma of the prostate? *J Clin Oncol* 2007; 25(24):3603-3608.	Review/Other-Tx	1 patient	To examine the cost effectiveness of proton beam radiation compared with current state-of-the art therapy in the treatment of patients with prostate cancer.	Analysis at 15 years resulted in an expected mean cost of proton beam therapy and IMRT of $63,511 and $36,808, and $64,989 and $39,355 for a 70-year-old and 60-year-old man respectively, with quality-adjusted survival of 8.54 and 8.12 and 9.91 and 9.45 QALYs, respectively. The incremental cost effectiveness ratio was calculated to be $63,578/QALY for a 70-year-old man and $55,726/QALY for a 60-year-old man.	4

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
42. Trofimov A, Nguyen PL, Coen JJ, et al. Radiotherapy treatment of early-stage prostate cancer with IMRT and protons: a treatment planning comparison. *Int J Radiat Oncol Biol Phys* 2007; 69(2):444-453.	Observational-Tx	10 patients	To compare IMRT with 3D-conformal proton therapy for early-stage prostate cancer, and explore the potential utility of intensity-modulated proton therapy.	At least 98% of the planning target volume received the prescription dose. IMRT plans yielded better dose conformity to the target, whereas proton plans achieved higher dose homogeneity and better sparing of rectum and bladder in the range below 30 Gy. Bladder volumes receiving more than 70 Gy (V70) were reduced, on average, by 34% with IMRT vs 3D-conformal proton therapy, whereas rectal V70 were equivalent. Equivalent uniform dose from 3D-conformal proton therapy and IMRT plans were indistinguishable within uncertainties for both bladder and rectum. With the use of small-angle lateral-oblique fields in 3D-conformal proton therapy and intensity-modulated proton therapy, the rectal V70 was reduced by up to 35% compared with the standard lateral configuration, whereas the bladder V70 increased by less than 10%.	2
43. Vargas C, Fryer A, Mahajan C, et al. Dose-volume comparison of proton therapy and intensity-modulated radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2008; 70(3):744-751.	Observational-Tx	10 patients	To evaluate data from proton protocol for low-risk prostate cancer.	All rectal and rectal wall volumes treated to 10-80 Gy (percentage of volume receiving 10-80 Gy [V(10)-V(80)]) were significantly lower with proton therapy ($P<0.05$). The rectal V(50) was reduced from 31.3% +/- 4.1% with IMRT to 14.6% +/- 3.0% with proton therapy for a relative improvement of 53.4% and an absolute benefit of 16.7% ($P<0.001$). The mean rectal dose decreased 59% with proton therapy ($P<0.001$). For the bladder and bladder wall, proton therapy produced significantly smaller volumes treated to doses of 10-35 Gy ($P<0.05$) with a nonsignificant advantage demonstrated for the volume receiving ≤60 Gy. The bladder V(30) was reduced with proton therapy for a relative improvement of 35.3% and an absolute benefit of 15.1% ($P=0.02$). The mean bladder dose decreased 35% with proton therapy ($P=0.002$).	2

Definitive External Beam Irradiation in Stage T1 and T2 Prostate Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
44. Coen JJ, Zietman AL, Rossi CJ, et al. Comparison of high-dose proton radiotherapy and brachytherapy in localized prostate cancer: a case-matched analysis. *Int J Radiat Oncol Biol Phys* 2012; 82(1):e25-31.	Observational-Tx	282 patients	To report a case-matched analysis comparing high-dose EBRT for prostate cancer delivered on Proton Radiation Oncology Group (PROG) 95-09, a randomized trial, with PPB over the same era.	Using the Phoenix definition, the 8-year biochemical failure rates were 7.7% and 16.1% for EBRT and brachytherapy, respectively (P=0.42). A stratified analysis was performed by risk group. In the EBRT group, 113 and 28 patients were low and intermediate risk, respectively. In the brachytherapy group, 118 and 23 were. When stratified by risk group, the biochemical failure rates were similar by either technique.	2
45. Sheets NC, Goldin GH, Meyer AM, et al. Intensity-modulated radiation therapy, proton therapy, or conformal radiation therapy and morbidity and disease control in localized prostate cancer. *JAMA* 2012; 307(15):1611-1620.	Observational-Tx	12,976 patients	To determine the comparative morbidity and disease control of IMRT, proton therapy, and CRT for primary prostate cancer treatment.	Use of IMRT vs CRT increased from 0.15% in 2000 to 95.9% in 2008. In propensity score-adjusted analyses (n=12,976), men who received IMRT vs CRT were less likely to receive a diagnosis of GI morbidities (absolute risk, 13.4 vs 14.7 per 100 person-years; RR, 0.91; 95% CI, 0.86-0.96) and hip fractures (absolute risk, 0.8 vs 1.0 per 100 person-years; RR, 0.78; 95% CI, 0.65-0.93) but more likely to receive a diagnosis of erectile dysfunction (absolute risk, 5.9 vs 5.3 per 100 person-years; RR, 1.12; 95% CI, 1.03-1.20). IMRT patients were less likely to receive additional cancer therapy (absolute risk, 2.5 vs 3.1 per 100 person-years; RR, 0.81; 95% CI, 0.73-0.89). In a propensity score-matched comparison between IMRT and proton therapy (n=1,368), IMRT patients had a lower rate of GI morbidity (absolute risk, 12.2 vs 17.8 per 100 person-years; RR, 0.66; 95% CI, 0.55-0.79). There were no significant differences in rates of other morbidities or additional therapies between IMRT and proton therapy.	2
46. Paulson DF, Lin GH, Hinshaw W, Stephani S. Radical surgery versus radiotherapy for adenocarcinoma of the prostate. *J Urol* 1982; 128(3):502-504.	Experimental-Tx	97 patients/ 56 received RT,/ 41 had RP	Randomized trial to compare radical surgery with RT for adenocarcinoma of the prostate.	38 patients assigned to RP and 52 assigned to RT received treatment. RP was more effective than megavoltage radiation in establishing disease control.	1
47. Hanks GE. More on the Uro-Oncology Research Group report of radical surgery vs. radiotherapy for adenocarcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 1988; 14(5):1053-1054.	Review/Other-Tx	N/A	Letter to editor criticizing a study by Paulson et al titled "The Uro-Oncology Group: Radical surgery vs RT for adenocarcinoma of the prostate."	N/A	4

Definitive External Beam Irradiation in Stage T1 and T2 Prostate Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
48. Taira AV, Merrick GS, Galbreath RW, Wallner KE, Butler WM. Natural history of clinically staged low- and intermediate-risk prostate cancer treated with monotherapeutic permanent interstitial brachytherapy. *Int J Radiat Oncol Biol Phys* 2010; 76(2):349-354.	Observational-Tx	463 patients	To evaluate the natural history of clinically staged low- and intermediate-risk prostate cancer treated with permanent interstitial seed implants as monotherapy.	The 12-year bPFS, cause-specific survival, and OS rates for the entire cohort were 97.1%, 99.7%, and 75.4%, respectively. Only pretreatment PSA level, percent positive biopsy cores, and minimum dose that covered 90% of the target volume were significant predictors of biochemical recurrence. The bPFS, cause-specific survival, and OS rates were 97.4%, 99.6%, and 76.2%, respectively, for low-risk patients and 96.4%, 100%, and 74.0%, respectively, for intermediate-risk patients. The bPFS rate was 98.8% for low-risk patients with high-quality implants vs 92.1% for those with less adequate implants ($P<0.01$), and it was 98.3% for intermediate-risk patients with high-quality implants vs 86.4% for those with less adequate implants ($P<0.01$).	3
49. Davis BJ, Horwitz EM, Lee WR, et al. American Brachytherapy Society consensus guidelines for transrectal ultrasound-guided permanent prostate brachytherapy. *Brachytherapy* 2012; 11(1):6-19.	Review/Other-Tx	N/A	To provide updated American Brachytherapy Society (ABS) guidelines for transrectal US-guided transperineal interstitial PPB.	Patients with high probability of organ-confined disease or limited extraprostatic extension are considered appropriate candidates for PPB monotherapy. Low-risk patients may be treated with PPB alone without the need for supplemental EBRT. High-risk patients should receive supplemental EBRT if PPB is used. Intermediate-risk patients should be considered on an individual case basis. Intermediate-risk patients with favorable features may appropriately be treated with PPB monotherapy but results from confirmatory clinical trials are pending. CT-based postimplant dosimetry performed within 60 days of the implant is considered essential for maintenance of a satisfactory quality assurance program. Postimplant CT-magnetic resonance image fusion is viewed as useful, but not mandatory.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
50. Frank SJ, Grimm PD, Sylvester JE, et al. Interstitial implant alone or in combination with external beam radiation therapy for intermediate-risk prostate cancer: a survey of practice patterns in the United States. *Brachytherapy* 2007; 6(1):2-8.	Review/Other-Tx	18 surveys	To understand and define the current patterns of care with respect to prostate brachytherapy for patients with intermediate-risk localized disease in the combined academic and community setting.	In the absence of perineural invasion, all of those surveyed would perform monotherapy for intermediate-risk patients, GS 7 (3+4) or PSA 10-20, with cT1c and <30% cores +. Up to 80% would perform monotherapy for patients with cT1c, GS 7 (4+3), and <30% cores +. 80% to 90% of physicians would perform an implant alone with cT2a and either a PSA of 10-20 or GS of 7 (3+4) and <30% cores +. 50% to 60% of those surveyed stated that they would treat a patient with cT2b disease, GS 7 (3+4), or PSA 11-20, with less than two-thirds of the biopsy cores positive in the absence of perineural invasion.	4
51. Kupelian PA, Mohan DS, Lyons J, Klein EA, Reddy CA. Higher than standard radiation doses (> or =72 Gy) with or without androgen deprivation in the treatment of localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2000; 46(3):567-574.	Observational-Tx	1,041 consecutive localized prostate cancer cases	To study the effect on bRFS and clinical DFS of radiation doses delivered to the prostate and periprostatic tissues for localized prostate cancer.	The 5- and 8-year bRFS rates were 61% (95% CI, 55%-65%) and 58% (95% CI, 51%-65%), respectively./ The 5-year bRFS rates for patients receiving radiation doses ≥72 Gy vs <72 Gy were 87% (95% CI, 82%-92%) and 55% (95% CI, 49%-60%), respectively./ The 8-year bRFS rates for patients receiving radiation doses ≥72 Gy vs <72 Gy were 87% (95% CI, 82%-92%) and 51% (95% CI, 44%-58%), respectively (P<0.001).	2
52. 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 hormonal therapy if indicated, results in improved BDFS in localized prostate adenocarcinoma.	IMRT patients had more advanced disease at baseline (P<.001). There was no difference in 5-year BDFS 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 hormonal therapy 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 BDFS, but treatment modality (P=.06) did not. Within the poor prognosis subset, treatment modality (P=.006) predicted BDFS.	2

Definitive External Beam Irradiation in Stage T1 and T2 Prostate Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
53. 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 distant metastases 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 to 0.65; P<.001). Results were similar for prostate cancer-specific mortality (HR, 0.32; 95% CI, 0.13 to 0.80; P=.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
54. Bagshaw MA, Cox RS, Ramback JE. Radiation therapy for localized prostate cancer. Justification by long-term follow-up. *Urol Clin North Am* 1990; 17(4):787-802.	Observational-Tx	1,031 patients treated with EBRT	Analysis of long-term follow-up data to examine what may be deduced regarding the radiocurability of prostatic cancer.	Survival patterns at 15 years after RT for patients with clinical stage A carcinoma of the prostate did not deviate significantly from those of an age-matched peer group. For patients with clinical stage B disease, survival was only 5% less at 15 years for the age-matched group of California men.	2
55. Hanks GE, Leibel SA, Krall JM, Kramer S. Patterns of care studies: dose-response observations for local control of adenocarcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 1985; 11(1):153-157.	Observational-Tx	574 patients	Patients treated 1973-1975 were retrospectively studied to determine relationship between dose and outcomes.	Dose-response relationship seen for T2 and T3 but not for T0 and T4 tumors. Variation in dose seems more a function of institution policy than disease characteristics and author recommend that this needs to change.	2
56. Lawton CA, Won M, Pilepich MV, et al. Long-term treatment sequelae following external beam irradiation for adenocarcinoma of the prostate: analysis of RTOG studies 7506 and 7706. *Int J Radiat Oncol Biol Phys* 1991; 21(4):935-939.	Observational-Tx	1,020 patients treated with EBRT	To describe the long-term toxicities associated with EBRT for patients treated in these trials.	At 7 years, 3.3% of patients had intestinal complications (Grade 3 or higher) and 7.7% had urinary complications. 0.6% of patients had bowel obstruction and 0.5% required some type of surgical intervention for their urinary problems. Authors conclude that low rate of morbidity argues for benefit of EBRT.	3
57. Perez CA, Lee HK, Georgiou A, Lockett MA. Technical factors affecting morbidity in definitive irradiation for localized carcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 1994; 28(4):811-819.	Observational-Tx	738 patients treated with definitive RT	A retrospective review to determine the relationship between certain technical aspects of therapy and patient morbidity.	Volume treated and, to a lesser extent, dose of irradiation at tolerance levels are important factors influencing significant morbidity in patients. Therefore, it's important to precisely determine optimal volumes and doses required to achieve the highest tumor control while minimizing morbidity.	2

Definitive External Beam Irradiation in Stage T1 and T2 Prostate Cancer
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
58. Pilepich MV, Asbell SO, Krall JM, et al. Correlation of radiotherapeutic parameters and treament related morbidity-analysis of RTOG study 77-06. *Int J Radiat Oncol Biol Phys* 1987; 13(7):1007-1012.	Experimental-Tx	453 cases	Update on treatment associated morbidity among patients enrolled in a phase III randomized trial comparing prostatic irradiation with pelvic irradiation followed by prostatic boost.	Pelvic irradiation was not associated with higher morbidity. Doses of >7000 cGy to the prostate were associated with rectal bleeding.	1
59. Pilepich MV, Krall JM, Sause WT, et al. Correlation of radiotherapeutic parameters and treatment related morbidity in carcinoma of the prostate--analysis of RTOG study 75-06. *Int J Radiat Oncol Biol Phys* 1987; 13(3):351-357.	Experimental-Tx	526 cases	Analysis of a randomized trial to identify and quantify the relationship with treatment volumes, doses, and techniques.	No correlation between the total dose to the regional lymphatics (ranging from 4400 to 5100 cGy) and the incidence of bowel and bladder injuries could be established.	1
60. Shipley WU, Prout GR, Jr., Coachman NM, et al. Radiation therapy for localized prostate carcinoma: experience at the Massachusetts General Hospital (1973-1981). *NCI Monogr* 1988; (7):67-73.	Observational-Tx	370 patients	To measure the success following irradiation in patients with clinically localized prostate carcinoma. The cumulative frequency curves using both univariate and multivariate analyses were evaluated.	Overall patient survival and probability of progression with distant metastases were significantly influenced by initial tumor stage and the degree of histologic differentiation. The results at 8 years are significantly better for patients with T2 (B) tumors (local regrowth in 8%, distant metastases in 18%) than for patients with T3-T4 (C) tumors (local regrowth in 28%, distant metastases in 60%). Patient tolerance of EBRT was carefully analyzed in 121 consecutively treated patients in 1980 and 1981 for subsequent radiation-related sequelae. Minor transient intestinal and urologic sequelae were observed in 21% and 23% of the patients, respectively.	2
61. Tucker SL, Thames HD, Michalski JM, et al. Estimation of alpha/beta for late rectal toxicity based on RTOG 94-06. *Int J Radiat Oncol Biol Phys* 2011; 81(2):600-605.	Observational-Tx	509 patients	To estimate alpha/beta, the parameter ratio from the linear-quadratic model, for Grade ≥2 late rectal toxicity among patients treated on RTOG 94-06; and to determine whether correcting the rectal dose-volume histogram for differences in dose per fraction, based on the linear-quadratic model, significantly improves the fit to these data of the Lyman-Kutcher-Burman normal-tissue complication probability model.	The analysis included 509 of the 1,084 patients enrolled on RTOG 94-06. The estimate of alpha/beta from the linear-quadratic-corrected Lyman-Kutcher-Burman model was 4.8 Gy, with 68% CI; 0.6 Gy to 46 Gy. The fit was not significantly different from the fit of the Lyman-Kutcher-Burman model based on physical dose to rectum (P=0.236).	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
62. Chen RC, Clark JA, Talcott JA. Individualizing quality-of-life outcomes reporting: how localized prostate cancer treatments affect patients with different levels of baseline urinary, bowel, and sexual function. *J Clin Oncol* 2009; 27(24):3916-3922.	Observational-Tx	409 patients	Although it is the most powerful predictor of early prostate cancer treatment-related complications and QOL outcomes, most studies do not stratify results by baseline function. Further, reporting functional outcomes as averaged numerical results may obscure informatively disparate courses. Using levels of treatment-related dysfunction, the study addresses these problems and presents the final QOL outcomes of this prospective cohort study of patients with early prostate cancer.	Different levels of baseline sexual, bowel, and urinary function produced distinctive treatment-related changes from baseline to 36 months. In general, the average scale increases in dysfunction were greatest among patients with normal baseline function, although patients with normal and intermediate baseline function had similar increases in sexual dysfunction. For patients whose baseline urinary obstruction/irritation was poor, both average scale scores and most patients' level of function improved after treatment, particularly after surgery.	1
63. Lu Y, Song PY, Li SD, et al. A method of analyzing rectal surface area irradiated and rectal complications in prostate conformal radiotherapy. *Int J Radiat Oncol Biol Phys* 1995; 33(5):1121-1125.	Observational-Tx	27 patients	To develop a method of analyzing rectal surface area irradiated and rectal complications in prostate CRT.	The observed occurrences of rectal complications appear to depend on the rectal surface area irradiated to a given dose level. The patient distribution of each toxicity grade exhibits a maximum as a function of percentage surface area irradiated, and the maximum moves to higher values of percentage surface area as the toxicity grade increases. The dependence of the normal tissue complication probabilities for the specified end point on dose and percentage surface area irradiated was fitted to Lyman's normal tissue complication probabilities model with a set of parameters. The curvature of the normal tissue complication probabilities as a function of the surface area suggests that the rectum is a parallel structured organ.	3
64. Dale E, Olsen DR, Fossa SD. Normal tissue complication probabilities correlated with late effects in the rectum after prostate conformal radiotherapy. *Int J Radiat Oncol Biol Phys* 1999; 43(2):385-391.	Observational-Tx	52 cancer prostate patients	To calculate different risk estimates of late effects in the rectum for a group of cancer prostate patients treated with CRT and correlate these estimates with the occurrences of late effects.	High-dose levels corresponding to small volume fractions of the cumulative dose-volume histograms were best correlated with the occurrences of late effects in the rectum as measured with questionnaires. Reducing the Lyman-Kutcher model's volume parameter, thus allowing small high-dose regions to determine the normal tissue complication probabilities, improved the correlation, but not beyond that of high-dose levels corresponding to small volume fractions of the cumulative dose-volume histograms.	3

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
65. Roach M, Winter K, Michalski JM, et al. Penile bulb dose and impotence after three-dimensional conformal radiotherapy for prostate cancer on RTOG 9406: findings from a prospective, multi-institutional, phase I/II dose-escalation study. *Int J Radiat Oncol Biol Phys* 2004; 60(5):1351-1356.	Observational-Tx	158 men	To assess the relationship between dose to bulb of penis and impotence.	Patients with penile dose >52.5 Gy had a greater risk of impotence (P=.039). In a multivariate analysis neither age, neither dose to the prostate, nor the use of hormonal therapy correlated with the risk of impotence. Only dose to the bulb was a predictor of impotence.	2
66. Hamilton AS, Stanford JL, Gilliland FD, et al. Health outcomes after external-beam radiation therapy for clinically localized prostate cancer: results from the Prostate Cancer Outcomes Study. *J Clin Oncol* 2001; 19(9):2517-2526.	Observational-Tx	497 patients	To assess effects of EBRT for prostate cancer among a population based cohort.	Sexual function was the most adversely affected QoL domain, with problems continuing to increase between 12 and 24 months. Bowel function problems increased at 6 months, but got better by 2 years. Despite the side effects, most patients were satisfied with therapy.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
67. Mantz CA, Song P, Farhangi E, et al. Potency probability following conformal megavoltage radiotherapy using conventional doses for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 1997; 37(3):551-557.	Observational-Tx	114 patients	To report the change in potency over time in an EBRT-treated population, determine the significantly predisposing health factors affecting potency in this population, and compare age and stage-matched potency rates with those of normal males and prostatectomy patients.	The actuarial probability of potency for all patients gradually decreased throughout post-RT follow-up. At months 1, 12, 24, and 36, potency rates were 98%, 92%, 75%, and 66%, respectively. For those patients who became impotent, the median time to impotence was 14 months. Factors identified from logistic regression analysis as significant predictors of post-EBRT impotence include pre-EBRT partial potency ($P<0.001$), vascular disease ($P<0.001$), and diabetes ($P=0.003$). Next, an actuarial plot of potency probability to patient age for the EBRT-treated population was compared to that obtained from the Massachusetts Male Aging Study of normal males. The two curves were not significantly different (log rank test, $P=0.741$) between ages 50 and 65. Finally, potency probability after follow-up of 1 year or more in EBRT-treated patients was stratified by age and substratified by clinical stage and then compared to similarly stratified potencies for patients treated with nerve-sparing RP. The prostatectomy data were derived from the pooled data of 6 large (total n=952), independent series conducted at academic centers. For patients older than 70 years, 79.1% of EBRT patients and 32.9% of nerve-sparing RP patients remained potent after treatment. For patients with stage B2 disease, 75.0% of EBRT patients and 49.3% of nerve-sparing RP patients remained potent after treatment. Overall EBRT patient potency was 76.1% vs 66.2% for nerve-sparing RP patients.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
68. Potosky AL, Legler J, Albertsen PC, et al. Health outcomes after prostatectomy or radiotherapy for prostate cancer: results from the Prostate Cancer Outcomes Study. *J Natl Cancer Inst* 2000; 92(19):1582-1592.	Observational-Tx	1,156 RP and 453 RT patients	To compare the effects of two treatments on urinary, bowel, and sexual functions and on general health-related QoL outcomes over a 2-year period following initial treatment.	Almost 2 years after treatment, men receiving RP were more likely than men receiving RT to be incontinent (9.6% vs 3.5%; P<.001) and to have higher rates of impotence (79.6% vs 61.5%; P<.001), although large, statistically significant declines in sexual function were observed in both treatment groups. In contrast, men receiving RT reported greater declines in bowel function than did men receiving RP. All of these differences remained after adjustments for propensity score. The treatment groups were similar in terms of general health-related QoL.	2
69. Alemozaffar M, Regan MM, Cooperberg MR, et al. Prediction of erectile function following treatment for prostate cancer. *JAMA* 2011; 306(11):1205-1214.	Observational-Tx	1,027 patients; prostatectomy (n=524), EBRT (n=241), or brachytherapy (n=262)	To predict long-term erectile function following prostate cancer treatment based on individual patient and treatment characteristics.	2-years after prostate cancer treatment, 368 (37% [95% CI, 34%-40%]) of all patients and 335 (48% [95% CI, 45%-52%]) of those with functional erections prior to treatment reported functional erections; 531 (53% [95% CI, 50%-56%]) of patients without penile prostheses reported use of medications or other devices for erectile dysfunction. Pretreatment sexual health related QoL score, age, serum PSA level, race/ethnicity, body mass index, and intended treatment details were associated with functional erections 2 years after treatment. Multivariable logistic regression models predicting erectile function estimated 2-year function probabilities from as low as 10% or less to as high as 70% or greater depending on the individual's pretreatment patient characteristics and treatment details. The models performed well in predicting erections in external validation among Cancer of the Prostate Strategic Urologic Research Endeavor [CaPSURE] cohort patients (areas under the receiver operating characteristic curve, 0.77 [95% CI, 0.74-0.80] for prostatectomy; 0.87 [95% CI, 0.80-0.94] for external RT; and 0.90 [95% CI, 0.85-0.95] for brachytherapy).	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
70. Incrocci L, Koper PC, Hop WC, Slob AK. Sildenafil citrate (Viagra) and erectile dysfunction following external beam radiotherapy for prostate cancer: a randomized, double-blind, placebo-controlled, cross-over study. *Int J Radiat Oncol Biol Phys* 2001; 51(5):1190-1195.	Experimental-Tx	60 patients-50 mg of sildenafil citrate (n=30) or placebo (n=30)	Randomized double-blind, placebo controlled, cross-over study to determine the efficacy of sildenafil citrate (Viagra) in patients with erectile dysfunction after 3D-CRT for prostate cancer.	Mean age was 68 years. All patients completed the study. For most questions of the IIEF questionnaire there was a significant increase in mean scores from baseline with sildenafil, but not with placebo. 90% of the patients needed a dose adjustment to 100 mg sildenafil. Side effects were mild or moderate. The treatment effect for Viagra was significant. Viagra is well tolerated and effective in improving erectile function of patients with erectile dysfunction after 3D-CRT for prostate cancer.	1
71. Weber DC, Bieri S, Kurtz JM, Miralbell R. Prospective pilot study of sildenafil for treatment of postradiotherapy erectile dysfunction in patients with prostate cancer. *J Clin Oncol* 1999; 17(11):3444-3449.	Observational-Tx	35 patients	Prospective pilot study. Phase I/II study of tolerability and efficacy of Viagra in prostate cancer patients.	30 patients (86%) completed the 6-week study. 77% of these patients had significantly improved erectile function, allowing recovery of full capacity for sexual intercourse. Of 27 patients not receiving concomitant hormone treatment, failure to respond was observed in only 4 patients (15%) compared with 4 (50%) of 8 patients receiving hormonal treatment during the study. The time course of response was gradual, with 40%, 57%, 66%, 69%, and 74% responding at weeks 1 through 5, respectively. Therapy was generally well tolerated. The most frequently reported side effects in patients were flushing (37%), transient headache (17%), and dyspepsia (9%). No patient reported priapism, and no cardiovascular event or death was observed. After response, 12 patients (34%) reported the ability to achieve and maintain an erection sufficient for intercourse in the absence of sildenafil (ie, 24 hours to 6 days after taking the medication).	2

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
72. Roach M, 3rd, Hanks G, Thames H, Jr., et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys* 2006; 65(4):965-974.	Review/Other-Tx	N/A	Consensus statement to revise the 1996 definition of biochemical failure after EBRT.	Concluded that 1) biochemical failure defined by a rise by 2 ng/mL or more above the nadir PSA after EBRT with or without hormonal therapy; and 2) the date of failure be determined "at call" (not backdated). They recommended that investigators be allowed to use the ASTRO Consensus Definition after EBRT alone (no hormonal therapy) with strict adherence to guidelines as to "adequate follow-up." The reported date of control should be listed as 2 years short of the median follow-up.	4
73. Jhaveri FM, Zippe CD, Klein EA, Kupelian PA. Biochemical failure does not predict overall survival after radical prostatectomy for localized prostate cancer: 10-year results. *Urology* 1999; 54(5):884-890.	Observational-Tx	1,132 consecutive patients; biochemical failure (n=213) biochemical failure (n=919)	Compare OS among patients with biochemical failure and patients without.	The 10-year OS rates for patients with biochemical failure (88%) vs no biochemical failure (93%) were similar (P=0.94). The survival rates of patients with biochemical failure were not statistically different than those of patients without biochemical failure when compared by age older than 65 years, preoperative PSA greater than 10 ng/mL, biopsy or specimen GS 7 or greater, clinical stage T2b-3, presence of extracapsular extension, positive surgical margins, and seminal vesicle invasion. Patients who received second-line treatment also had a similar 10-year OS rate (86%, P=0.97). For the 213 patients with biochemical failure, the metastasis-free survival rate at 10 years was 74%. The OS rate for patients with distant metastasis (56%) was markedly lower (P<0.001) than for those without distant metastasis.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
74. D'Amico AV, Moul JW, Carroll PR, Sun L, Lubeck D, Chen MH. Surrogate end point for prostate cancer-specific mortality after radical prostatectomy or radiation therapy. *J Natl Cancer Inst* 2003; 95(18):1376-1383.	Observational-Tx	8,669 patients treated with surgery (5,918 men) or radiation (2,751 men)	To evaluate the hypothesis that a short post-treatment PSA doubling time after RT is a surrogate end point for prostate cancer-specific mortality by analyzing two multi-institutional databases.	The post-treatment PSA doubling time was statistically significantly associated with time to prostate cancer-specific mortality and with time to all-cause mortality (all P(Cox)<.001). However, the treatment received was not statistically significantly associated with time to prostate cancer-specific mortality after PSA-defined disease recurrence for patients with a PSA doubling time of <3 months (P(Cox)=.90) and for patients with a PSA doubling time of 3 months or more (P(Cox)=.28) when controlling for the specific value of the PSA doubling time. Furthermore, after a PSA-defined recurrence, a PSA doubling time of <3 months was statistically significantly associated with time to prostate cancer-specific mortality (median time = 6 years; HR = 19.6, 95% CI, 12.5 to 30.9).	2
75. Freedland SJ, Humphreys EB, Mangold LA, et al. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. *JAMA* 2005; 294(4):433-439.	Observational-Tx	379 men	To define risk factors for prostate cancer death following RP and to develop tables to risk stratify for prostate cancer-specific survival.	Median survival had not been reached after 16 years of follow-up after biochemical recurrence. Prostate-specific doubling time (<3.0 vs 3.0-8.9 vs 9.0-14.9 vs ≥15.0 months), pathological GS ≤7 vs 8-10), and time from surgery to biochemical recurrence (≤3 vs >3 years) were all significant risk factors for time to prostate-specific mortality. Using these 3 variables, tables were constructed to estimate the risk of prostate cancer-specific survival at year 15 after biochemical recurrence.	2
76. Cox JD, Stoffel TJ. The significance of needle biopsy after irradiation for stage C adenocarcinoma of the prostate. *Cancer* 1977; 40(1):156-160.	Review/Other-Tx	38 consecutive patients	To determine whether the results of needle biopsy are meaningful for stage C patients undergoing definitive EBRT.	Positive biopsy rate correlated only with the interval after irradiation; 60% at 6 months, 37% at 1 year, 30% at 18 months, and approximately 19% after two and one-half years. There was no correlation of biopsy results with pre-irradiation estrogen or orchiectomy, with time-dose-fractionation relationships, or with prognosis.	4
77. Scardino PT. The prognostic significance of biopsies after radiotherapy for prostatic cancer. *Semin Urol* 1983; 1(4):243-252.	Review/Other-Tx	N/A	Review historical background leading to the prevalent conclusion that a positive biopsy has no clinical significance.	Evidence is available to document the grave prognostic significance of a positive biopsy after definitive RT for prostate cancer.	4

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78. Freiha FS, Bagshaw MA. Carcinoma of the prostate: results of post-irradiation biopsy. *Prostate* 1984; 5(1):19-25.	Review/Other-Tx	146 patients	To determine whether post-irradiation biopsy is meaningful. Retrospective study of patients with localized disease who were surgically staged and underwent EBRT.	72% of those with a positive biopsy went on to develop metastatic disease compared with 24% of those with a negative biopsy showing the prognostic value of biopsy in this population.	4
79. Scardino PT, Wheeler TM. Local control of prostate cancer with radiotherapy: frequency and prognostic significance of positive results of postirradiation prostate biopsy. *NCI Monogr* 1988; (7):95-103.	Review/Other-Tx	510 patients	To examine the frequency and prognostic significance of positive results of post-irradiation biopsy performed at a sufficient interval after RT.	Poor prognosis associated with a positive biopsy result was found within almost every subset of stage, grade, or nodal status examined although the results varied.	4
80. Crook J, Malone S, Perry G, Bahadur Y, Robertson S, Abdolell M. Postradiotherapy prostate biopsies: what do they really mean? Results for 498 patients. *Int J Radiat Oncol Biol Phys* 2000; 48(2):355-367.	Observational-Tx	498 men	To determine the time course for histologic tumor resolution and to correlate biopsy results with PSA and clinical outcome.	Median follow-up is 54 months (range 13-131). 175 patients (34%) had prior hormonal therapy for a median of 5 months (range 1-60). Clinical stage distribution was T1b: 46; T1c: 50; T2a: 115; T2b/c: 170; T3: 108; T4: 11; Tx: 1. Distribution by GS was: 28% GS 2-4; 42%: 5-6; 18%: 7; and 12%: 8-10. Seventy-one men have died, 26 of prostate cancer and 45 of other causes. Actuarial failure-free survival by T stage at 5 years is T1b: 78%; T1c: 76%; T2a: 60%; T2b/c: 55%; T3: 30%; and T4: 0%. Actuarial freedom from local failure at 5 years is T1b: 83%; T1c: 88%; T2a: 72%; T2b/c: 66%; T3: 58%; and T4: 0%. The proportion of indeterminate biopsies decreases with time, being 33% for biopsy 1, 24% for biopsy 2, 18% for biopsy 3, and 7% for biopsy 4. 30% of indeterminate biopsies resolved to bNED status, regardless of the degree of RT effect, 18% progressed to local failure, and 34% remained as biopsy failures with indeterminate status within the time frame of this report. Positive staining for proliferation markers was associated with both subsequent local failure and also any type of failure. In multivariate analysis, only PSA nadir (P=0.0002) and biopsy status at 24-36 months (P=0. 0005) were independent predictors of outcome.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
81. 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 20 ng/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). Biochemical failure, distant metastases, 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 two groups. The incidence of grade 3 or higher hormone-related toxic effects was less than 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
82. 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 androgen suppression therapy 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 androgen suppression therapy to RT resulted in increased OS in men with localized but unfavorable-risk prostate cancer.	1

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83. 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 neoadjuvant ADT 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 neoadjuvant ADT group, and 267 in the 6-month neoadjuvant ADT group) after a median follow-up of 10.6 years (IQR 6.9-11.6). Compared with RT alone, 3 months of neoadjuvant ADT 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 neoadjuvant ADT 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 neoadjuvant ADT had no effect on distant progression (0.89, 0.60-1.31; P=0.550), prostate cancer-specific mortality (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 neoadjuvant ADT decreased distant progression (0.49, 0.31-0.76; P=0.001), prostate cancer-specific mortality (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 neoadjuvant ADT within the first 5 years after randomization.	1
84. 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

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85. 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 two 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), biochemical failure (68.1% vs 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
86. Nanda A, Chen MH, Braccioforte MH, Moran BJ, D'Amico AV. Hormonal therapy use for prostate cancer and mortality in men with coronary artery disease-induced congestive heart failure or myocardial infarction. *JAMA* 2009; 302(8):866-873.	Observational-Tx	5,077 men	To assess whether NHT use affects the risk of all-cause mortality in men with prostate cancer and coronary artery disease-induced congestive heart failure or myocardial infarction, coronary artery disease risk factors, or no comorbidity.	NHT use was not associated with an increased risk of all-cause mortality in men with no comorbidity (9.6% vs 6.7%, adjusted HR, 0.97; 95% CI, 0.72-1.32; P=.86) or a single coronary artery disease risk factor (10.7% vs 7.0%, adjusted HR, 1.04; 95% CI, 0.75-1.43; P=.82) after median follow-ups of 5.0 and 4.4 years, respectively. However, for men with coronary artery disease-induced congestive heart failure or myocardial infarction, after a median follow-up of 5.1 years, NHT use was significantly associated with an increased risk of all-cause mortality (26.3% vs 11.2%, adjusted HR, 1.96; 95% CI, 1.04-3.71; P=.04).	2

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
87. 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.	Review/Other-Tx	4,141 patients	To perform a systematic review and meta-analysis of randomized trials to determine whether ADT is associated with cardiovascular mortality, prostate cancer-specific mortality, 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 (255/2,200 vs 252/1,941 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 4,805 patients from 11 trials with overall death data, ADT was associated with lower prostate cancer-specific mortality (443/2,527 vs 552/2,278 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 (1,140/2,527 vs 1,213/2,278 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).	4
88. Brenner DJ, Hall EJ. Fractionation and protraction for radiotherapy of prostate carcinoma. *Int J Radiat Oncol Biol Phys* 1999; 43(5):1095-1101.	Review/Other-Tx	N/A	To investigate whether current fractionation and brachytherapy protraction schemes for the treatment of prostatic cancer with radiation are optimal, or could be improved.	Prostatic cancers appear significantly more sensitive to changes in fractionation than most other cancers. The estimated alpha/beta value is 1.5 Gy [0.8, 2.2]. This result is not too surprising as there is a documented relationship between cellular proliferative status and sensitivity to changes in fractionation, and prostatic tumors contain exceptionally low proportions of proliferating cells.	4

Definitive External Beam Irradiation in Stage T1 and T2 Prostate Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
89. Fowler J, Chappell R, Ritter M. Is alpha/beta for prostate tumors really low? *Int J Radiat Oncol Biol Phys* 2001; 50(4):1021-1031.	Review/Other-Tx	17 clinical papers	To review updated clinical data and present somewhat different calculations to estimate alpha/beta. Three methods of estimating alpha/beta were employed. First, a simple two-step graphical comparison of isoeffective doses from external beam and implant modalities was made, to see which value of alpha/beta predicted the observed identity of biologic effect. Second, the same data were subjected to Direct Analysis (maximum likelihood estimation), from which an estimate of alpha/beta and also of the T(12) of repair of sublethal damage in the tumors (both with CIs) were obtained. Third, preliminary clinical data comparing two different sizes of high-dose boost doses were analyzed in which significantly different bNED was observed at 2 years.	The second method gave the definitive result of alpha/beta = 1.49 Gy (95% CI 1.25-1.76) and T(12) = 1.90 h (95% CI 1.42-2.86 h). The first method gave a range from 1.4 to 1.9 Gy and showed that if mean or median dose were used instead of prescribed dose, the estimate of alpha/beta would be substantially below 1 Gy. The third method, although based on early follow-up, was consistent with low values of alpha/beta in the region of 2 Gy or below. The estimate for T(12) is the first value reported for prostate tumors in situ.	4
90. Wang JZ, Guerrero M, Li XA. How low is the alpha/beta ratio for prostate cancer? *Int J Radiat Oncol Biol Phys* 2003; 55(1):194-203.	Review/Other-Tx	N/A	To present a comprehensive analysis of the updated clinical data to derive a self-consistent set of parameters for the linear-quadratic model.	Based on the analysis of clinical data and a consideration of repopulation effect, we have derived a self-consistent set of linear-quadratic parameters for prostate cancer: alpha = 0.15 +/- 0.04 Gy(-1), alpha/beta = 3.1 +/- 0.5 Gy. The analysis indicates the half-time of sublethal damage repair to be in the range from 0 to 90 min with a best estimate of 16 min. The best estimate of clonogenic cell numbers in prostate tumors is found to range from 10(6) to 10(7) according to the patient risk level. These values are more realistic than those derived previously (only 10-100).	4
91. Thames HD, Bentzen SM, Turesson I, Overgaard M, Van den Bogaert W. Time-dose factors in radiotherapy: a review of the human data. *Radiother Oncol* 1990; 19(3):219-235.	Review/Other-Tx	N/A	To review data on linear-quadratic parameters for human normal tissues and tumors.	The values for alpha/beta (fractionation sensitivity, or recovery capacity) for early and late reactions in human normal tissues are consistent with results from experimental animals. For breast treatments direct analysis indicates that for early reactions alpha/beta is in the range 7 to 11 Gy, while for late effects it is in the range 2 to 4 Gy.	4

Definitive External Beam Irradiation in Stage T1 and T2 Prostate Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
92. Miles EF, Lee WR. Hypofractionation for prostate cancer: a critical review. *Semin Radiat Oncol* 2008; 18(1):41-47.	Review/Other-Tx	N/A	A critical review that examines the clinical experience with hypofractionation.	Several prospective trials indicate that toxicity is limited with sophisticated dose delivery and compact clinical target volume to planning target volume margins, but the single-arm nature of these trials precludes definitive statements on efficacy. Several large randomized trials comparing conventional fractionation to hypofractionation are ongoing and are described. Until these trials are completed and the results submitted for rigorous peer review, the notion that alpha/beta for prostate cancer is low remains an unconfirmed hypothesis.	4
93. King C. Stereotactic body radiotherapy for prostate cancer: current results of a phase II trial. *Front Radiat Ther Oncol* 2011; 43:428-437.	Observational-Tx	69 patients	To review data from the Stanford phase II trial. The trial examined the use of hypofractionation of stereotactic body RT for prostate cancer.	To date, excellent PSA responses have been observed in patients with lower-risk disease selected for treatment and receiving 36.25 Gy in 5 fractions. To date, sexual QoL outcomes have also been approximately comparable to other RT approaches. Rates of late GI and GU toxicity have been relatively low and generally comparable to dose-escalated approaches using conventional fractionation.	2
94. Arcangeli G, Saracino B, Gomellini S, et al. A prospective phase III randomized trial of hypofractionation versus conventional fractionation in patients with high-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2010; 78(1):11-18.	Experimental-Tx	168 patients	To compare the toxicity and efficacy of hypofractionated (62 Gy/20 fractions/5 weeks, 4 fractions per week) vs conventional fractionation RT (80 Gy/40 fractions/8 weeks) in patients with high-risk prostate cancer.	The median (range) follow-up was 32 (8-66) and 35 (7-64) months in the hypofractionation and conventional fractionation arms, respectively. No difference was found for late toxicity between the two treatment groups, with 3-year Grade 2 rates of 17% and 16% for GI and 14% and 11% for GU in the hypofractionation and conventional fractionation groups, respectively. The 3-year freedom from biochemical failure rates were 87% and 79% in the hypofractionation and conventional fractionation groups, respectively (P=0.035). The 3-year freedom from biochemical failure rates in patients at a very high risk (ie, pretreatment PSA >20 ng/mL, GS ≥8, or T ≥2c), were 88% and 76% (P=0.014) in the former and latter arm, respectively. The multivariate Cox analysis confirmed fractionation, pretreatment PSA, and GS as significant prognostic factors.	1

Definitive External Beam Irradiation in Stage T1 and T2 Prostate Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
95. Dearnaley D, Syndikus I, Sumo G, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: preliminary safety results from the CHHiP randomised controlled trial. *Lancet Oncol* 2012; 13(1):43-54.	Experimental-Tx	457 patients; 153 allocated to 74 Gy in 37 daily fractions of 2 Gy, 153 allocated to 60 Gy in 20 daily fractions of 3 Gy, 151 allocated to 57 Gy in 19 daily fractions of 3 Gy	To present a pre-planned preliminary safety analysis of side-effects in stages 1 and 2 of a randomized trial comparing standard and hypofractionated RT.	With 50.5 months median follow-up (IQR 43.5-61.3), 6 (4.3%; 95% CI 1.6-9.2) of 138 men in the 74 Gy group had bowel toxicity of grade 2 or worse on the RTOG scale at 2 years, as did 5 (3.6%; 1.2-8.3) of 137 men in the 60 Gy group, and 2 (1.4%; 0.2-5.0) of 143 men in the 57 Gy group. For bladder toxicities, 3 (2.2%; 0.5-6.2) of 138 men, 3 (2.2%; 0.5-6.3) of 137, and none (0.0%; 97.5% CI 0.0-2.6) of 143 had scores of grade 2 or worse on the RTOG scale at 2 years.	1
96. Pollack A, Hanlon AL, Horwitz EM, et al. Dosimetry and preliminary acute toxicity in the first 100 men treated for prostate cancer on a randomized hypofractionation dose escalation trial. *Int J Radiat Oncol Biol Phys* 2006; 64(2):518-526.	Experimental-Tx	100 men	To compare 76 Gy in 38 fractions (Arm I) to 70.2 Gy in 26 fractions (Arm II) using IMRT. The study hypothesis was that freedom from biochemical failure would be increased without increasing late toxicity. The dosimetry and acute side effects for the first 100 men randomized are described.	The mean planning target volume doses for Arms I and II were 81.1 and 73.8 Gy. There were no differences in overall maximum acute GI or GU toxicity acutely. However, there was a slight but significant increase in Arm II GI toxicity during Weeks 2, 3, and 4. In multivariate analyses, only the combined rectal dose-volume histograms parameter of V65 Gy/V50 Gy was significant for GI toxicity and the bladder volume for GU toxicity.	1

Definitive External Beam Irradiation in Stage T1 and T2 Prostate Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
97. Pollack A, Walker G, Buyyounouski M, et al. Five Year Results of a Randomized External Beam Radiotherapy Hypofractionation Trial for Prostate Cancer. *International Journal of Radiation Oncology*Biology*Physics* 2011; 81(2):S1.	Experimental-Tx	303 patients; 152 assigned to receive conventional-IMRT and 151 to receive hypo-IMRT	To compare 76 Gy in conventional 2.0 Gy fractions (conventional-IMRT) to 70.2 Gy in 2.7 Gy fractions (hypo-IMRT), which was estimated to be equivalent to 84.4 Gy in 2.0 Gy fractions. Study hypothesized that using hypofractionation to deliver the equivalent of an 8 Gy difference in 2 Gy fractions would significantly improve biochemical failure without increasing bladder or rectal side effects.	No significant differences were seen between the treatment arms in terms of the distribution of patients by T-category, GS, pretreatment initial PSA, use of ADT or length of ADT. There were 41 biochemical failures with 20 in the conventional-IMRT group and 21 in the hypo-IMRT group. 6 biochemical failures occurred within 6.5 months of either local-regional failure or distant metastasis, with the earliest event time used as failure time. Competing risk events are comprised of 1 local-regional failure, 2 distant metastasis, and 4 deaths. The 5-year CI rates of biochemical failure were 14.4% (95% CI, 8.8%–21.5%) for conventional-IMRT and 13.9% (95% CI, 8.4%–20.9%) for hypo-IMRT. Rates for local-regional failure/distant metastasis were 1.0% and 1.3% for conventional-IMRT and hypo-IMRT at 5 years. Considering any failure, the 5-year CI rates for conventional-IMRT were 15.4% (95% CI, 9.5%–22.7%) and 15.3% (95% CI, 9.5%–22.4%) for hypo-IMRT. There were no statistically significant differences in late toxicity between the arms. The Grade 2 or higher toxicities for the conventional-IMRT and hypo-IMRT arms were 8.9 and 13.8 (P=0.2) for GU and 4.1 and 5.9% (P=0.5) for GI.	1

Definitive External Beam Irradiation in Stage T1 and T2 Prostate Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
98. Kuban DA, Nogueras-Gonzalez GM, Hamblin L, et al. Preliminary Report of a Randomized Dose Escalation Trial for Prostate Cancer using Hypofractionation. *International Journal of Radiation Oncology*Biology*Physics* 2010; 78(3):S58-S59.	Experimental-Tx	204 patients; 102 patients on the conventional-IMRT arm and 102 on hypo-IMRT arm	To report outcome and toxicity for patients treated on a phase III randomized radiation dose-escalation trial for localized prostate cancer using hypofractionation.	There were 8 PSA failures using the ASTRO definition (as defined by protocol) on the conventional-IMRT arm and 4 on the hypo-IMRT arm for 5 year failure-free results of 92% and 96% for all patients, 96% and 97% for low risk patients, and 90% and 95% for intermediate risk patients, with no statistically significant differences. Using the nadir +2 definition, there were 5 PSA failures on the conventional-IMRT arm and 4 on the hypo-IMRT arm for 5-year PSA failure-free rates of 94%-97%. There have been neither clinical failures nor prostate cancer deaths to date and no difference in OS. 4 patients on the conventional-IMRT arm had Grade 2 GI toxicity and 1 Grade 3 for 5-year actuarial rates of 5% and 1%. On the hypo-IMRT arm, there were 9 patients with Grade 2 GI toxicity and 2 with Grade 3, 11% and 3%, respectively. Differences between arms were not statistically significant, for Grade 2 and Grade 3, although there was a trend toward higher toxicity for hypo-IMRT patients for all toxicity combined, Grades 1-4, HR = 1.68, P=0.058. There were 15 Grade 2 GU toxicities on each arm, and 1 Grade 3 GU toxicity with conventional-IMRT for a 5-year Grade 2/3 toxicity rate of 19% for both arms. The Grade 3 GI toxicities were due to 3 laser coagulation procedures and the Grade 3 GU event was a urethral stricture. There were no Grade 4 complications. Seventy-five percent of GI and GU toxicities had resolved within 1 year.	1

Definitive External Beam Irradiation in Stage T1 and T2 Prostate Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
99. Norkus D, Miller A, Kurtinaitis J, et al. A randomized trial comparing hypofractionated and conventionally fractionated three-dimensional external-beam radiotherapy for localized prostate adenocarcinoma : a report on acute toxicity. *Strahlenther Onkol* 2009; 185(11):715-721.	Experimental-Tx	91 patients	To compare acute GI and GU toxicity between patient groups with localized prostate adenocarcinoma treated with CFRT and hypofractionated 3D-CRT.	No acute grade 3 or 4 toxicities were observed. The grade 2 GU acute toxicity proportion was significantly lower in the hypofractionated 3D-CRT arm: 19.1% vs 47.7% (chi(2)-test, P=0.003). The grade 2 GU acute toxicity-free survival was significantly better in the hypofractionated 3D-CRT arm (log-rank test, P=0.008). The median duration of overall GI acute toxicity was shorter with hypofractionated 3D-CRT: 3 compared to 6 weeks with CFRT (median test, P=0.017).	1
100. Norkus D, Miller A, Plieskiene A, Janulionis E, Valuckas KP. A randomized trial comparing hypofractionated and conventionally fractionated three-dimensional conformal external-beam radiotherapy for localized prostate adenocarcinoma: a report on the first-year biochemical response. *Medicina (Kaunas)* 2009; 45(6):469-475.	Experimental-Tx	91 patients	To describe the first-year biochemical PSA response of patients enrolled in a single-institution randomized trial comparing hypofractionated and CFRT EBRT.	Proportions of patients reaching nPSA1 were 50% and 54.5% in the CFRT and hypofractionated RT treatment arms, respectively (chi-square P=0.843). Percentages of patients reaching nPSA05 were 25% and 18.2%, respectively (chi-square P=0.621). Hypofractionated RT schedule induces biochemical response rates comparable to those in the CFRT schedule during the first-year follow-up.	1
101. King CR, Brooks JD, Gill H, Presti JC, Jr. Long-term outcomes from a prospective trial of stereotactic body radiotherapy for low-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2012; 82(2):877-882.	Observational-Tx	67 patients	To present the results of a prospective trial of stereotactic body RT for prostate cancer with long-term patient-reported toxicity and tumor control rates.	Median follow-up was 2.7 years. There were no grade 4 toxicities. RTOG Grade 3, 2, and 1 bladder toxicities were seen in 3% (2 patients), 5% (3 patients), and 23% (13 patients) respectively. Dysuria exacerbated by urologic instrumentation accounted for both patients with Grade 3 toxicity. Urinary incontinence, complete obstruction, or persistent hematuria was not observed. Rectal Grade 3, 2, and 1 toxicities were seen in 0, 2% (1 patient), and 12.5% (7 patients), respectively. Persistent rectal bleeding was not observed. Low-grade toxicities were substantially less frequent with QOD vs QD dose regimen (P=0.001 for GI and P=0.007 for GU). There were two PSA, biopsy-proven failures with negative metastatic workup. Median PSA at follow-up was 0.5 +/- 0.72 ng/mL. The 4-year Kaplan-Meier PSA relapse-free survival was 94% (95% CI, 85%-102%).	2

Definitive External Beam Irradiation in Stage T1 and T2 Prostate Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
102. McBride SM, Wong DS, Dombrowski JJ, et al. Hypofractionated stereotactic body radiotherapy in low-risk prostate adenocarcinoma: preliminary results of a multi-institutional phase 1 feasibility trial. *Cancer* 2012; 118(15):3681-3690.	Observational-Tx	45 patients	A report by authors on their multi-institutional experience with extreme hypofractionated stereotactic RT for early stage disease.	The median follow-up for surviving patients was 44.5 months (range, 0-62 months). The bPFS rate at 3 years was 97.7%. The median PSA declined from 4.9 ng/mL at diagnosis to 0.2 ng/mL at last follow-up, and the median percentage PSA decline at 12 months was 80%. 9 patients experienced at least 1 PSA bounce ≥0.4 ng/mL, and 4 patients experienced 2 PSA bounces. The median time to first PSA bounce was 11.6 months (range, 7.2-18.2 months), and the mean percentage PSA bounce was 1.07 ng/mL. There was 1 episode of late grade 3 urinary obstruction, and there were 2 episodes of late grade 3 proctitis. There was a significant late decline in SHIM and EPIC sexual scores and a small, late decline in the EPIC Bowel domain score.	3
103. Lukka H, Hayter C, Julian JA, et al. Randomized trial comparing two fractionation schedules for patients with localized prostate cancer. *J Clin Oncol* 2005; 23(25):6132-6138.	Experimental-Tx	936 men randomly assigned to long arm (470) and short arm (466)	To compare two dose fractionation schemes (a shorter 4-week radiation schedule vs a longer 6.5-week schedule).	The median follow-up time was 5.7 years. At 5 years, the biochemical or clinical failure probability was 52.95% in the long arm and 59.95% in the short arm (difference = -7.0%; 90% CI, -12.6% to -1.4%), favoring the long arm. No difference in 2-year postradiotherapy biopsy or in OS was detected between the arms. Acute toxicity was found to be slightly higher in the short arm (11.4%) compared with the long arm (7%; difference = -4.4%; 95% CI, -8.1% to -0.6%); however, late toxicity was similarly low in both arms (3.2%).	1

Definitive External Beam Irradiation in Stage T1 and T2 Prostate Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
104. Yeoh EE, Botten RJ, Butters J, Di Matteo AC, Holloway RH, Fowler J. Hypofractionated versus conventionally fractionated radiotherapy for prostate carcinoma: final results of phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2011; 81(5):1271-1278.	Experimental-Tx	217 patients randomized to either hypofractionated (n=108) or the conventional (n=109) dose schedule	To evaluate the long-term efficacy and toxicity of a hypofractionated (55 Gy in 20 fractions within 4 weeks) vs a CFRT (64 Gy in 32 fractions within 6.5 weeks) dose schedule for RT for localized carcinoma of the prostate.	The whole group has now been followed for a median of 90 months (range, 3-138). Of the 217 patients, 85 developed biochemical relapse (nadir PSA level+2 mug/L), 36 in the hypofractionated and 49 in the conventional group. The bRFS, but not overall, survival at 90 months was significantly better with the hypofractionated (53%) than with the conventional (34%) schedule. GI and GU toxicity persisted 60 months after RT and did not differ between the two dose schedules. Multivariate analyses revealed that the conventional schedule was of independent prognostic significance, not only for biochemical failure, but also for an increased risk of worse GU symptoms at 4 years.	1

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.

Dx = Diagnostic

Tx = Treatment

Abbreviations Key

3D-CRT = 3D-confromal radiation therapy
ADT = Androgen deprivation therapy
AHT = Adjuvant hormonal therapy
BDFS = Biochemical disease-free survival
bNED = Biochemical no evidence of disease
bPFS = Biochemical progression-free survival
BPH = Benign prostatic hyperplasia
bRFS = Biochemical relapse-free survival
CFRT = Conventionally fractionated radiation therapy
CI = Confidence interval
CRT = Conformal radiation therapy
CT = Computed tomography
DFS = Disease-free survival
DRE = Digital rectal examination
EBRT = External-beam radiation therapy
EFRT = Extended field radiation therapy
GI = Gastrointestinal
GS = Gleason Score
GU = Genitourinary
HR = Hazard ratio
IGRT = Image-guided radiotherapy
IMRT = Intensity-modulated radiotherapy
IQR = Interquartile range
NCHT = Neoadjuvant and concurrent hormonal therapy
NHT = Neoadjuvant hormonal therapy
OS = Overall survival
PPB = Permanent prostate brachytherapy
PFS = Progression-free survival
PLND = Pelvic lymph node dissection
PPI = Prostate implant brachytherapy
PSA = Prostate-specific antigen
QALY = Quality-adjusted life-years
QoL = Quality-of-life
RP= Radical prostatectomy
RR= Relative risk
RT = Radiation therapy
US = Ultrasound
WPRT = Whole pelvic radiotherapy