

**High Dose Rate Brachytherapy for Prostate Cancer  
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. Brenner DJ, Hall EJ. Fractionation and protraction for radiotherapy of prostate carcinoma. <i>Int J Radiat Oncol Biol Phys</i> 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. HDR brachytherapy would be a highly appropriate modality for treating prostate cancer. Appropriately designed HDR brachytherapy regimens would be expected to be as efficacious as low dose rate, but with added advantages of logistic convenience and more reliable dose distributions. Similarly, EBRT for prostate cancer can be designed using larger doses per fraction; appropriately designed hypofractionation schemes would be expected to maintain current levels of tumor control and late sequelae, but with reduced acute morbidity, together with the logistic and financial advantages of fewer numbers of fractions.	4

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2. Martinez AA, Gonzalez J, Ye H, et al. Dose escalation improves cancer-related events at 10 years for intermediate- and high-risk prostate cancer patients treated with hypofractionated high-dose-rate boost and external beam radiotherapy. <i>Int J Radiat Oncol Biol Phys</i> 2011; 79(2):363-370.	Observational-Tx	472 patients	To evaluate the 10-year outcomes of intermediate- and high-risk prostate cancer patients treated with a prospective dose escalation hypofractionated trial of pelvic EBRT with a HDR brachytherapy boost.	Median follow-up was 8.2 years (range, 0.4-17 years). The 10-year biochemical failure rate of 43.1% vs 18.9%, (P<0.001), the clinical failure rate of 23.4% vs 7.7%, (P<0.001), and the distant metastasis of 12.4% vs 5.7%, (P=0.028) were all significantly better for the high-dose level group. On Cox multivariate analysis, higher biologically equivalent dose levels (P=0.017; HR = 0.586), pretreatment PSA assays (P<0.001, HR = 1.022), and GSs (P=0.004) were significant variables for reduced biochemical failure. Higher dose levels (P=0.002; HR, 0.397) and GSs (P<0.001) were significant for clinical failure. Grade 3 GU complications were 2% and 3%, respectively, and grade 3 gastrointestinal complication was <0.5%. This prospective trial using pelvic EBRT with HDR boost and hypofractionated dose escalation demonstrates a strong dose-response relationship for intermediate- and high-risk prostate cancer patients. The improvement at 10 years for locoregional control with higher radiation doses (biologically equivalent dose, >268 Gy) has significantly decreased biochemical and clinical failures as well as distant metastasis.	2

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<p>3. Martinez AA, Gustafson G, Gonzalez J, et al. Dose escalation using conformal high-dose-rate brachytherapy improves outcome in unfavorable prostate cancer. <i>Int J Radiat Oncol Biol Phys</i> 2002; 53(2):316-327.</p>	<p>Observational-Tx</p>	<p>207 patients</p>	<p>Prospective trial of pelvic EBRT interdigitated with dose-escalating conformal HDR prostate brachytherapy to overcome radioresistance for patients with unfavorable prostate cancer.</p>	<p>The median age was 69 years. The mean follow-up for the group was 4.4 years, and for the low and high-dose levels, it was 7.0 and 3.4 years, respectively. The actuarial 5-year biochemical control rate was 74%, and the OS, cause-specific survival, and DFS rate was 92%, 98%, and 68%, respectively. The 5-year biochemical control rate for the low-dose group was 52%; the rate for the high-dose group was 87% (P&lt;0.001). Improvement occurred in the cause-specific survival in favor of the brachytherapy high-dose level (P=0.014). On multivariate analysis, a low-dose level, higher GS, and higher nadir value were associated with increased biochemical failure. The Radiation Therapy Oncology Group Grade 3 gastrointestinal/GU complications ranged from 0.5% to 9%. The actuarial 5-year impotency rate was 51%. Pelvic EBRT interdigitated with transrectal ultrasound-guided real-time conformal HDR prostate brachytherapy boost is both a precise dose delivery system and a very effective treatment for unfavorable prostate cancer. We demonstrated an incremental beneficial effect on biochemical control and cause-specific survival with higher doses. These results, coupled with the low risk of complications, the advantage of not being radioactive after implantation, and the real-time interactive planning, define a new standard for treatment.</p>	<p>1</p>

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4. Martinez AA, Kestin LL, Stromberg JS, et al. Interim report of image-guided conformal high-dose-rate brachytherapy for patients with unfavorable prostate cancer: the William Beaumont phase II dose-escalating trial. <i>Int J Radiat Oncol Biol Phys</i> 2000; 47(2):343-352.	Observational-Tx	142 patients	To analyze experience treating patients with unfavorable prostate cancer in a prospective phase II dose-escalating trial of EBRT integrated with conformal HDR brachytherapy boosts. This interim report discusses treatment outcome and prognostic factors using this treatment approach.	The pretreatment PSA level was $\geq 10.0$ ng/ml in 51% of patients. The biopsy GS was $\geq 7$ in 58% of cases, and 75% of cases were clinical stage T2b or higher. Despite the high frequency of these poor prognostic factors, the actuarial biochemical control rate was 89% at 2 years and 63% at 5 years. On multivariate analysis, a higher pretreatment PSA level, higher GS, higher PSA nadir level, and shorter time to nadir were associated with biochemical failure. In the entire population, 14 patients (10%) experienced clinical failure at a median interval of 1.7 years (range: 0.2-4.5 years) after completing RT. The 5-year actuarial clinical failure rate was 22%. The 5-year actuarial rates of local failure and distant metastasis were 16% and 14%, respectively. For all patients, the 5-year DFS, OS, and cause-specific survival rates were 89%, 95%, and 96%, respectively. The 5-year actuarial rate of RTOG Grade 3 late complications was 9% with no patient experiencing Grade 4 or 5 acute or late toxicity. Pelvic EBRT in combination with image-guided conformal HDR brachytherapy boosts appears to be an effective treatment for patients with unfavorable prostate cancer with minimal associated morbidity. Our dose-escalating trial will continue.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
5. Hsu IC, Bae K, Shinohara K, et al. Phase II trial of combined high-dose-rate brachytherapy and external beam radiotherapy for adenocarcinoma of the prostate: preliminary results of RTOG 0321. <i>Int J Radiat Oncol Biol Phys</i> 2010; 78(3):751-758.	Observational-Tx	125 patients	To estimate the rate of late Grade 3 or greater GU and gastrointestinal adverse events after treatment with EBRT and prostate HDR brachytherapy.	Adverse events data were available for 112 patients at analysis. The pretreatment characteristics of the patients were as follows: Stage T1c-T2c, 91%; Stage T3a-T3b, 9%; PSA level ≤10 ng/mL, 70%; PSA level >10 but ≤20 ng/mL, 30%; and GS 2-6, 10%; GS 7, 72%; and GS 8-10, 18%. At a median follow-up of 29.6 months, three acute and four late Grade 3 GU/gastrointestinal adverse events were reported. The estimated rate of late Grade 3-5 GU and gastrointestinal adverse events at 18 months was 2.56%. This is the first prospective, multi-institutional trial of CT-based HDR brachytherapy and EBRT. The technique and doses used in the present study resulted in acceptable levels of adverse events.	2
6. Morton GC, Loblaw DA, Sankrecha R, et al. Single-fraction high-dose-rate brachytherapy and hypofractionated external beam radiotherapy for men with intermediate-risk prostate cancer: analysis of short- and medium-term toxicity and quality of life. <i>Int J Radiat Oncol Biol Phys</i> 2010; 77(3):811-817.	Observational-Tx	123 patients	To determine the short- and medium-term effects of a single HDR brachytherapy fraction of 15 Gy and hypofractionated EBRT for prostate cancer.	Acute grade 2 and 3 GU toxicity occurred in 62% and 1.6% of patients, respectively, and acute grade 2 gastrointestinal toxicity occurred in 6.5% of patients. No grade 3 late toxicity has occurred: 47% of patients had grade 2 GU and 10% of patients had grade 2 gastrointestinal toxicity. Median International Prostate Symptom Score rose from 5 at baseline to 12 at 1 month and returned to 7 at 3 months. Of the total number of patients who were initially potent (International Index of Erectile Function, >21), 8% of patients developed mild to moderate dysfunction, and 27% of patients developed severe erectile dysfunction. Baseline Expanded Prostate Cancer Index Composite bowel, urinary, and sexual bother scores decreased by 9, 7, and 19 points, respectively, at 1 year. No patient has experienced biochemical failure, and 16 of the first 17 biopsy results showed no malignancy. Treatment is well tolerated in the short and medium term, with low toxicity and encouraging early indicators of disease control.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
7. Morton G, Loblaw A, Cheung P, et al. Is single fraction 15 Gy the preferred high dose-rate brachytherapy boost dose for prostate cancer? <i>Radiother Oncol</i> 2011; 100(3):463-467.	Observational-Tx	Single fraction protocol: 123 patients; Standard fractionation protocol: 60 patients	To compare outcomes with a single fraction HDR boost to that with a standard fractionated boost in intermediate risk prostate cancer.	With a median follow-up of 45 and 72 months, respectively, the biochemical DFS was 95.1% and 97.9% in the Single and Standard Fractionation trials (P=0.3528). 2-year prostate biopsy was positive in only 4% and 8%, respectively. There was no difference in late urinary or rectal toxicity rates or in health-related quality of life between the 2 protocols.	1
8. Erickson BA, Demanes DJ, Ibbott GS, et al. American Society for Radiation Oncology (ASTRO) and American College of Radiology (ACR) practice guideline for the performance of high-dose-rate brachytherapy. <i>Int J Radiat Oncol Biol Phys</i> 2011; 79(3):641-649.	Review/Other-Tx	N/A	Practice guidelines for the performance of HDR brachytherapy.	N/A	4
9. Monroe AT, Faricy PO, Jennings SB, Biggers RD, Gibbs GL, Peddada AV. High-dose-rate brachytherapy for large prostate volumes (> or =50cc)-Uncompromised dosimetric coverage and acceptable toxicity. <i>Brachytherapy</i> 2008; 7(1):7-11.	Observational-Tx	54 patients	To review a single-institution experience using HDR brachytherapy in patients with large-volume prostate glands $\geq 50$ cc).	The median D(90) (minimal dose to 90% of the prostate) was 109% of prescription dose (range, 95%-115%) and the median V(100) (volume receiving 100% of the dose) was 96% (range, 90%-99%). V(150) ranged from 10% to 35%, with a median value of 18.3%. Six patients (11%) required temporary placement of a urinary catheter for acute obstructive symptoms after brachytherapy. With a median follow-up of 1.8 years, there has been a single case of Grade 2 gastrointestinal toxicity and 1 patient has developed a bulbo-urethral stricture requiring dilation. There have been no cases of rectal bleeding. Large prostate volume is not a contraindication to HDR brachytherapy. Excellent dosimetric coverage can be attained with acceptable acute toxicity.	2

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10. Yoshida K, Kuroda S, Yoshida M, et al. New implant technique for separation of the seminal vesicle and rectal mucosa for high-dose-rate prostate brachytherapy. <i>Brachytherapy</i> 2007; 6(3):180-186.	Observational-Tx	23 patients	To evaluate a new technique using an anchor applicator for HDR-ISBT of prostate cancer.	Implantation of the applicator on the posterior side of the seminal vesicle was successful for 43/46 seminal vesicle (93%). The median percentage of the seminal vesicles receiving the prescribed dose was 41% (range 11%-86%). Only one case of acute Grade 2 toxicity (3%) was seen. Our anchor applicator technique for HDR-ISBT can separate the seminal vesicle from the rectum. This is the first report of dose-volume histogram analysis of the seminal vesicle for HDR-ISBT.	3
11. Peddada AV, Jennings SB, Faricy PO, Walsh RA, 3rd, White GA, Monroe AT. Low morbidity following high dose rate brachytherapy in the setting of prior transurethral prostate resection. <i>J Urol</i> 2007; 178(5):1963-1967.	Review/Other-Tx	28 patients	To review a single institution experience with HDR brachytherapy in patients who underwent prior transurethral prostate resection.	Dosimetric goals were adequately achieved in all patients with a median minimal dose to 90% of the prostate of 109% of the prescription dose (range 100% to 117%). The median volume receiving 100% of the prescribed dose was 95% (range 87.9% to 100%) Three patients (11%) required temporary urinary catheter placement for acute obstructive symptoms after brachytherapy. At a median follow-up of 2.5 years there was 1 case each of grade 1 rectal proctitis, grade 1 hemorrhage and grade 2 cystitis. Two patients had worsening of existing grade 1 urge incontinence to grade 2. Patients with a higher baseline American Urological Association score demonstrated significantly improved scores over those with lower baseline scores (<15) at least 1 year after treatment. HDR brachytherapy with careful attention to dosimetry is a reasonable treatment option for patients who have undergone prior transurethral prostate resection with the expectation of low morbidity.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
12. Hoskin PJ, Motohashi K, Bownes P, Bryant L, Ostler P. High dose rate brachytherapy in combination with external beam radiotherapy in the radical treatment of prostate cancer: initial results of a randomised phase three trial. <i>Radiother Oncol</i> 2007; 84(2):114-120.	Experimental-Tx	220 patients	Randomized phase III trial to compare EBRT alone with a dose escalated schedule using HDR brachytherapy.	With a median follow up of 30 months (range 3-91) a significant improvement in actuarial biochemical RFS is seen in favor of the combined brachytherapy schedule (P=0.03). A lower incidence of acute rectal discharge was seen in the brachytherapy group (P=0.025) and other acute and late toxicities were equivalent. Patients randomized to brachytherapy had a significantly better FACT-P score at 12 weeks (P=0.02). The use of HDR brachytherapy in combination with EBRT resulted in an improved biochemical RFS compared to EBRT alone with less acute rectal toxicity and improved quality of life in this randomized trial.	1
13. Hoskin PJ, Bownes PJ, Ostler P, Walker K, Bryant L. High dose rate afterloading brachytherapy for prostate cancer: catheter and gland movement between fractions. <i>Radiother Oncol</i> 2003; 68(3):285-288.	Review/Other-Tx	20 consecutive patients	To evaluate catheter and gland movement between fractions.	The mean interfraction movement of catheters as measured by external length was <1 mm, but within the prostate on consecutive CT scans there was a mean interfraction movement of 11.5 mm away from the prostate base. This has a significant impact on implant dosimetry as measured by D90 and the COIN index, unless corrected by repositioning the catheters.	4



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14. Kim Y, Hsu IC, Pouliot J. Measurement of craniocaudal catheter displacement between fractions in computed tomography-based high dose rate brachytherapy of prostate cancer. <i>J Appl Clin Med Phys</i> 2007; 8(4):2415.	Review/Other-Tx	10 consecutive patients	To measure the cranio-caudal displacement of catheters occurring between consecutive fractions of transrectal ultrasound guided HDR prostate brachytherapy.	The average (range) magnitude of caudal catheter displacement was 2.7 mm (-6.0 to 13.5 mm) for bony marker method and 5.4 mm (-3.75 to 18.0 mm) for center of two gold markers method, respectively. The measurement data obtained from bony marker and center of two gold markers methods verified that both prostate movement and catheter displacement occurred independently between fractions. The most anterior and medial two catheters (catheter position 8 and 12) had the greatest tendency to be displaced in the caudal direction because they were located at the most distant position from the fulcrum, susceptible to the rotation of the dental putty in lateral plane due to the movement of patient legs between fractions. In conclusion, the use of both bony marker and center of two gold markers methods can demonstrate the prostate and catheter movement relative to the bony marker between fractions. We found a pattern of catheter displacement using our technique. Based on our finding further improvement of our results may be possible by modification of our current technique.	4

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<p>15. Foster W, Cunha JA, Hsu IC, Weinberg V, Krishnamurthy D, Pouliot J. Dosimetric impact of interfraction catheter movement in high-dose rate prostate brachytherapy. <i>Int J Radiat Oncol Biol Phys</i> 2011; 80(1):85-90.</p>	<p>Observational-Tx</p>	<p>15 patients</p>	<p>To evaluate the impact of interfraction catheter movement on dosimetry in prostate HDR brachytherapy.</p>	<p>Mean interfraction catheter displacement was 5.1 mm. The initial plan on day 2, the mean prostate V100 (volume receiving 100 Gy or more) decreased from 93.8% to 76.2% (P&lt;0.01). Rectal V75 went from 0.75 cm (3) to 1.49 cm(3) (P&lt;0.01). A re-optimization resulted in a mean prostate V100 of 88.1%, closer to the initial plan (P=0.05). Mean rectal V75 was also improved with a value of 0.59 cm(3). There was no significant change in bladder and urethra dose on day 2. A mean interfraction catheter displacement of 5.1 mm results in a significant decrease in prostate V100 and an increase in rectum dose. A re-optimization before the second treatment improves dose distribution.</p>	<p>3</p>

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16. Ghadjar P, Gwerder N, Madlung A, et al. Use of gold markers for setup in image-guided fractionated high-dose-rate brachytherapy as a monotherapy for prostate cancer. <i>Strahlenther Onkol</i> 2009; 185(11):731-735.	Observational-Tx	35 patients	To investigate the use of gold markers for X-ray-based setup and position control between the single fractions.	Median follow-up was 3 years. The mean change of applicators positions compared to baseline varied substantially between HDR brachytherapy fractions, being 1.4 mm before fraction 1 (range, -4 to 2 mm), -13.1 mm before fraction 2 (range, -36 to 0 mm), -4.1 mm before fraction 3 (range, -21 to 9 mm), and -2.6 mm at fraction 4 (range, -16 to 9 mm). The original position of the applicators could be readjusted easily prior to each fraction in every patient. In 18 patients (51%), the applicators were at least once readjusted >10 mm, however, acute or late grade $\geq 2$ GU toxicity was not increased (P=1.0) in these patients. Caudal position shifts up to 36 mm were observed. Gold markers represent a valuable tool to ensure setup accuracy and precise dose delivery in fractionated HDR brachytherapy monotherapy of prostate cancer.	2

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17. Simnor T, Li S, Lowe G, et al. Justification for inter-fraction correction of catheter movement in fractionated high dose-rate brachytherapy treatment of prostate cancer. <i>Radiother Oncol</i> 2009; 93(2):253-258.	Observational-Tx	20 consecutive patients	To evaluate inter-fraction correction of catheter movement in fractionated HDR brachytherapy treatment of prostate cancer.	Compared to the first fraction (f1) the mean inter-fraction caudal movement relative to the prostate base was 7.9 mm (f2) (range 0-21 mm) and 3.9 mm (f3) (range 0-25.5 mm). Planning target volume D90% was reduced without movement correction by a mean of 27.8% (f2) and 32.3% (f3), compared with 5.3% and 5.1%, respectively, with catheter movement correction. Dose to 2 cc of the rectum increased by a mean of 0.69 (f2) and 0.76 Gy (f3) compared with an increase of 0.03 and 0.04 Gy, respectively, with correction. The urethra V12 also increased by a mean of 0.36 (f2) and 0.39 Gy (f3) compared with 0.06 and 0.16 Gy, respectively, with correction. Inter-fraction correction for catheter movement using pretreatment imaging is critical to maintain the quality of an implant. Without movement correction there is significant risk of tumor under-dosage and normal tissue over-dosage. The findings of this study justify additional imaging between fractions in order to carry out correction.	3
18. Yoshida K, Yamazaki H, Nose T, et al. Needle applicator displacement during high-dose-rate interstitial brachytherapy for prostate cancer. <i>Brachytherapy</i> 2010; 9(1):36-41.	Review/Other-Tx	64 patients	To evaluate an effective ambulatory technique in HDR-ISBT for prostate cancer.	The median displacement distance for all applicators was 7 mm (range, -14 to 24), and that of each treatment schedule was 4, 6, and 9 mm for 38, 49, and 54 Gy, respectively. Of the 776 applicators, displacement of >10 mm was seen in 198 (26%) applicators and >15 mm in 57 (7%) applicators. Body height (P<0.0001) and anticoagulant usage (P<0.0001) were significant factors influencing displacement. CT scanning should be performed daily during treatment for checking the position of the applicator to detect and rectify the issue of displacement.	4

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19. Yoshioka Y, Konishi K, Sumida I, et al. Monotherapeutic high-dose-rate brachytherapy for prostate cancer: five-year results of an extreme hypofractionation regimen with 54 Gy in nine fractions. <i>Int J Radiat Oncol Biol Phys</i> 2011; 80(2):469-475.	Observational-Tx	112 patients	To evaluate an extreme hypofractionation regimen with 54 Gy in 9 fractions provided by HDR brachytherapy as monotherapy for prostate cancer by reporting 5-year clinical results.	All the patients safely completed the treatment regimen. The 5-year PSA failure-free, local control, DFS, and OS rate was 83%, 97%, 87%, and 96%, respectively. The 5-year PSA failure-free rate for low-, intermediate-, and high-risk patients was 85% (95% CI, 66%-100%), 93% (95% CI, 83%-100%), and 79% (95% CI, 69%-89%), respectively. The significant prognostic factors for PSA failure were the initial PSA level (P=.029) and younger age (P=.019). The maximal toxicities observed were Grade 3 using the Common Terminology Criteria for Adverse Events, version 3.0, for both acute and late toxicity (6 and 3 patients had acute and late Grade 3 toxicity, respectively). Late Grade 2 toxicity was observed in 13 patients. Monotherapeutic HDR brachytherapy with an extreme hypofractionation regimen of 54 Gy in 9 fractions associated with hormonal therapy was feasible, and its toxicity was acceptable. The interim tumor control rate at a median 5.4 years was promising, even for patients with locally advanced disease.	2
20. Yoshioka Y, Nose T, Yoshida K, et al. High-dose-rate interstitial brachytherapy as a monotherapy for localized prostate cancer: treatment description and preliminary results of a phase I/II clinical trial. <i>Int J Radiat Oncol Biol Phys</i> 2000; 48(3):675-681.	Observational-Tx	22 patients	To improve results for localized prostate cancer, a prospective clinical trial of hyperfractionated Iridium-192 HDR brachytherapy as a monotherapy was initiated.	Median follow-up time was 31 months. HDR brachytherapy as a monotherapy was well-tolerated. No significant intra- or peri-operative complications occurred. No patient experienced acute toxicity of grade 3 or more. PSA levels normalized in 95% of patients within 20 months after irradiation. Four-year clinical and biochemical RFS rates were 95% and 55%, respectively. Acute toxicity with this method was acceptable. Further patient accrual and longer follow-up will allow comparison to other techniques.	2

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<p>21. Martinez AA, Pataki I, Edmundson G, Sebastian E, Brabbins D, Gustafson G. Phase II prospective study of the use of conformal high-dose-rate brachytherapy as monotherapy for the treatment of favorable stage prostate cancer: a feasibility report. <i>Int J Radiat Oncol Biol Phys</i> 2001; 49(1):61-69.</p>	<p>Review/Other-Tx</p>	<p>41 patients</p>	<p>To evaluate the technical feasibility and tolerance of image-guided transperineal conformal-HDR brachytherapy as the sole treatment modality for favorable, localized cancer of the prostate, and to analyze possible intrafraction and interfraction volume changes in the prostate gland which may affect dosimetric quality.</p>	<p>Median age was 64 years (range 51-79). Stage distribution was 27 T1c patients and 14 T2a patients. Three patients had GS of 5; 34 had GS of 6; 4 patients had GS of 7. Median pretreatment PSA was 4.7 ng/ml (range 0.8-13.3). All patients tolerated the treatment well with minimal discomfort. For 23 patients, data on volume changes in the gland during the implant were tabulated. They demonstrated a mean prostate volume of 30.7 cc before any manipulation with needles, 37.0 cc at the end of fraction 1, and 38.2 cc at the end of fraction 4. In addition, for those 10 patients prospectively evaluated for required adjustments, the overall mean adjustment between fraction 1 and fraction 2 was 2.0 cm, between fraction 2 and 3 was 0.4 cm, and between fractions 3 and 4 was 0.4 cm. For 10 consecutive patients, the average prescriptions dose -D90 for fractions 1 and 4 were 104% and 100%, respectively. The corresponding average urethral D10 for fractions 1 and 4 were 122% and 132%. Conformal HDR-ISBT as monotherapy for early cancer of the prostate was feasible and well tolerated by 41 patients treated. Changes in interfraction prostate volume do not appear to be significant enough to warrant modification of dosimetry for each fraction. Both excellent dose coverage of the prostate gland and low urethral dose are achieved as measured by dose-volume histograms.</p>	<p>4</p>

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22. Corner C, Rojas AM, Bryant L, Ostler P, Hoskin P. A Phase II study of high-dose-rate afterloading brachytherapy as monotherapy for the treatment of localized prostate cancer. <i>Int J Radiat Oncol Biol Phys</i> 2008; 72(2):441-446.	Observational-Tx	110 patients	To evaluate HDR brachytherapy monotherapy for prostate cancer.	Seven patients required urethral catheterization at 2 weeks; 3 receiving 34 Gy, 1 receiving 36 Gy, and 3 receiving 31.5 Gy. Only 3 patients remained catheterized at 12 weeks. RTOG 1 and 2 gastrointestinal toxicity at 2 weeks was seen in 61%, 68%, and 77%, respectively. Grade 3 bladder toxicity was seen in 2 patients at 6 months, 1 each from the 36 Gy and 31.5 Gy arms. One patient from the 31.5-Gy cohort reported Grade 2 bowel toxicity at 6 months. PSA, stratified for androgen deprivation therapy and no-androgen deprivation therapy patients ranged from 16.1-22.9 microg/L and 11.1-12.5 microg/L, respectively. This fell at 12 months to 0.2-0.6 microg/L and 0.5-1.4 microg/L, respectively. No PSA relapses have yet been seen with a median follow-up of 30 months (34 Gy), 18 months (36 Gy), and 11.8 months (31.5 Gy). Early results suggest an excellent biochemical response with no differences seen in acute and late toxicity between doses of 34 Gy/4 fractions, 36 Gy/four fractions, or 31.5 Gy/3 fractions.	1
23. Ghilezan M, Martinez A, Gustason G, et al. High-dose-rate brachytherapy as monotherapy delivered in two fractions within one day for favorable/intermediate-risk prostate cancer: preliminary toxicity data. <i>Int J Radiat Oncol Biol Phys</i> 2012; 83(3):927-932.	Observational-Tx	94 patients	To report the toxicity profile of HDR-brachytherapy as monotherapy in a Human Investigation Committee-approved study consisting of a single implant and two fractions (12 Gy x 2) for a total dose of 24 Gy, delivered within 1 day.	The median follow-up was 17 months (range, 6-40.5). Most patients had Grade 0-1 acute toxicity. The Grade 2 acute GU toxicity was mainly frequency/urgency (13%), dysuria (5%), hematuria, and dribbling/hesitancy (2%). None of the patients required a Foley catheter at any time; however, 8% of the patients experienced transient Grade 1 diarrhea. No other acute gastrointestinal toxicities were found. The most common chronic toxicity was Grade 2 urinary frequency/urgency in 16% of patients followed by dysuria in 4% of patients; 2 patients had Grade 2 rectal bleeding and 1 had Grade 4, requiring laser treatment.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
24. Demanes DJ, Martinez AA, Ghilezan M, et al. High-dose-rate monotherapy: safe and effective brachytherapy for patients with localized prostate cancer. <i>Int J Radiat Oncol Biol Phys</i> 2011; 81(5):1286-1292.	Observational-Tx	298 patients	To report the disease control and toxicity of HDR monotherapy from California Endocurietherapy and William Beaumont Hospital in low- and intermediate-risk prostate cancer patients.	The median follow-up time was 5.2 years. The median age of the patients was 63 years, and the median value of the pretreatment prostate-specific antigen was 6.0 ng/mL. The 8-year results were 99% local control, 97% biochemical control (nadir +2), 99% distant metastasis-free survival, 99% cause-specific survival, and 95% OS. Toxicity was scored per event, meaning that an individual patient with more than one symptom was represented repeatedly in the morbidity data table. GU toxicity consisted of 10% transient Grade 2 urinary frequency or urgency and 3% Grade 3 episode of urinary retention. Gastrointestinal toxicity was <1%.	2
25. Prada PJ, Jimenez I, Gonzalez-Suarez H, Fernandez J, Cuervo-Arango C, Mendez L. High-dose-rate interstitial brachytherapy as monotherapy in one fraction and transperineal hyaluronic acid injection into the perirectal fat for the treatment of favorable stage prostate cancer: treatment description and preliminary results. <i>Brachytherapy</i> 2012; 11(2):105-110.	Observational-Tx	40 consecutive patients	To evaluate the technical feasibility, acute and late GU toxicity, and gastrointestinal toxicity after HDR brachytherapy as monotherapy in one fraction with transperineal hyaluronic acid injection into the perirectal fat to displace the rectal wall away from the radiation sources to decrease rectal toxicity.	All patients tolerated the implantation procedure very well with minimal discomfort. No intraoperative or perioperative complications occurred. Acute toxicity Grade 2 or more was not observed in any patients. No chronic toxicity has been observed after treatment. Logistic regression showed that the late Grade 1 GU toxicity was associated with D(90) (P=0.050). The 32-month actuarial biochemical control was 100% and 88%, respectively (P=0.06) for low- and intermediate-risk groups.	2
26. Hatiboglu G, Pinkawa M, Vallee JP, Hadaschik B, Hohenfellner M. Application technique: placement of a prostate-rectum spacer in men undergoing prostate radiation therapy. <i>BJU Int</i> 2012; 110(11 Pt B):E647-652.	Review/Other-Tx	29 patients	To describe the technique used to apply a hydrogel spacer between the prostate and rectum so as to decrease the radiation dose to the rectum in patients with prostate cancer who are undergoing RT.	Hydrogel injection resulted in mean additional prostate-rectum space relative to baseline of 9.87 (5.92) mm. The mean procedure time, as measured by needle insertion and removal, was 6.3 (3.2) minutes. The relative reduction in rectal V70 was 60.6%. There were no unanticipated adverse events associated with the hydrogel procedure or the hydrogel.	4



**High Dose Rate Brachytherapy for Prostate Cancer  
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
27. Chade DC, Eastham J, Graefen M, et al. Cancer control and functional outcomes of salvage radical prostatectomy for radiation-recurrent prostate cancer: a systematic review of the literature. <i>Eur Urol</i> 2012; 61(5):961-971.	Review/Other-Tx	40 articles	To critically analyze the currently available evidence on salvage radical prostatectomy as to patient selection, predictive oncologic factors, surgical technique, cancer control, surgical complications, functional outcomes, and comparison to other salvage therapies using using Medline, Embase, and Web of Science databases.	Positive surgical margins in salvage radical prostatectomy varied from 43% to 70% in earlier publications vs 0%-36% in recent publications, and pathologic organ-confined disease was found in 22%-53% vs 44%-73% in earlier vs recent publications. Biochemical recurrence-free probability after salvage radical prostatectomy ranged from 47% to 82% at 5 years and from 28% to 53% at 10 years. Cancer-specific survival and OS varied from 70% to 83% and 54% to 89% at 10 years. Pre-salvage radical prostatectomy PSA value and prostate biopsy GS were the strongest prognostic risk factors for progression-free survival, organ-confined disease, and cancer-specific survival. Open, laparoscopic, and robotic techniques were shown to be feasible in the hands of experienced surgeons. The most frequent complications included anastomotic stricture (7%-41%) followed by rectal injury (0%-28%). Major complications (modified Clavien classification grade 3-5) varied from 0% to 25%. Most complications were less frequent in more recent series, except for anastomotic stricture. The majority of patients had erectile dysfunction prior to salvage radical prostatectomy (50%-91%) and 80%-100% after salvage radical prostatectomy. Urinary continence ranged from 21% to 90% after surgery. Limitations of this review include the absence of prospective studies and lack of comparative analyses between salvage radical prostatectomy and other therapies.	4

**High Dose Rate Brachytherapy for Prostate Cancer  
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
28. Mouraviev V, Spiess PE, Jones JS. Salvage cryoablation for locally recurrent prostate cancer following primary radiotherapy. <i>Eur Urol</i> 2012; 61(6):1204-1211.	Review/Other-Tx	N/A	To review current salvage cryoablation (SCA) outcomes in patients with locally recurrent prostate cancer (PCa) following primary radiation therapy.	Salvage cryoablation is a feasible and efficacious treatment modality, especially using third-generation technology, whereby the biochemical DFS is estimated to be between 50% and 70% at 5-years follow-up in properly selected patients. Severe complications such as rectourethral fistulas are significantly less common over the last decade than was reported in the past. Because there are no prospective, randomized studies and the definitions of PSA failure vary among many studies, comparisons between these different salvage modalities are limited in terms of cancer-specific outcomes. Nevertheless, in recent years, tertiary care referral centers for prostate cryotherapy have reported their treatment outcomes using rigorous treatment end points and morbidity grading systems, dramatically improving the quality of reported clinical data. Consequently, favorable predictors of treatment outcomes have been identified.	4

**High Dose Rate Brachytherapy for Prostate Cancer  
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
29. Lukka H, Waldron T, Chin J, et al. High-intensity focused ultrasound for prostate cancer: a systematic review. <i>Clin Oncol (R Coll Radiol)</i> 2011; 23(2):117-127.	Review/Other-Tx	34 clinical studies of HIFU	Systematic literature review to evaluate the evidence comparing HIFU with standard treatment in patients with localised prostate cancer.	29 evaluated HIFU as the primary treatment and 5 examined HIFU as salvage treatment for recurrence after RT. In most studies the outcomes used to determine efficacy were negative biopsy rates or PSA levels. Among the 29 studies of HIFU as the primary treatment, negative biopsy rates ranged from 35% to 95% in 21 studies, a PSA nadir of $\leq 0.5$ ng/ml ranged from 55% to 91% in 10 studies and mean PSA nadirs ranged from 0 to 1.9 ng/ml in 17 studies. Five studies reported 5-year DFS rates ranging from 55% to 95%. Among 5 studies of HIFU as salvage treatment, negative biopsy rates ranged from 73% to 84% in 4 studies, a PSA nadir of $\leq 0.5$ ng/ml ranged from 57% to 66% in 3 studies and mean PSA nadirs were 1.97 and 2.38 ng/ml in 2 studies, respectively. Current evidence on HIFU use in prostate cancer patients is of low quality, rendering it difficult to draw conclusions about its efficacy.	4
30. Goffinet DR, Martinez A, Freiha F, et al. 125Iodine prostate implants for recurrent carcinomas after external beam irradiation: preliminary results. <i>Cancer</i> 1980; 45(11):2717-2724.	Review/Other-Tx	14 patients	Preliminary results from 125-Iodine prostate implants for recurrent carcinomas after EBRT.	Clinical local control has been obtained in 11/14 patients for follow-up periods of 6 to 36 months. 8 remain without evidence of disease, but 2/3 patients whose pelvic lymph nodes were involved by carcinoma have developed distant metastases. Complications, consisting of cystoproctitis, urinary incontinence, or the development of a vesicorectal fistula occurred in 4/14 patients. These complications were noted only in those patients who had implantation of high intensity 125I seeds (greater than 0.50 mCi) into large prostatic volumes ( $\geq 50$ cc). No complications occurred in patients who received lower intensity 125I seed implants in smaller prostatic volumes.	4

**High Dose Rate Brachytherapy for Prostate Cancer  
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
31. Burri RJ, Stone NN, Unger P, Stock RG. Long-term outcome and toxicity of salvage brachytherapy for local failure after initial radiotherapy for prostate cancer. <i>Int J Radiat Oncol Biol Phys</i> 2010; 77(5):1338-1344.	Observational-Tx	37 men: local failure after initial prostate RT (32 EBRT and 5 brachytherapy)	To describe long-term outcomes and toxicity after salvage brachytherapy for local failure after initial RT for prostate cancer.	Median follow-up was 86 months (range, 2-156). The median dose to 90% of the prostate volume was 122 Gy (range, 67-166). The 10-year freedom from biochemical failure and cancer-specific survival were 54% and 96%, respectively. On univariate analysis, PSA >10 ng/mL at initial diagnosis was significantly associated with freedom from biochemical failure (P=0.01), and there were trends for both age <70 years (P=0.08) and PSA <6 ng/mL (P=0.08) at the time of salvage brachytherapy. On multivariate analysis, only presalvage PSA <6 ng/mL (P=0.046) was significantly associated with improved freedom from biochemical failure. There were three Grade 3 toxicities and one Grade 4 toxicity. Pelvic lymph node dissection before salvage brachytherapy was the only variable significantly associated with Grade ≥2 toxicity (P=0.03).	2
32. Grado GL, Collins JM, Kriegshauser JS, et al. Salvage brachytherapy for localized prostate cancer after radiotherapy failure. <i>Urology</i> 1999; 53(1):2-10.	Observational-Tx	49 patients	To evaluate the effectiveness and morbidity of salvage brachytherapy for locally recurrent or persistent prostate cancer after RT failure.	The actuarial rate of local prostate cancer control was 98% (95% CI; 94% to 99%). Actuarial disease-specific survival at 3 and 5 years was 89% (95% CI; 73% to 96%) and 79% (95% CI; 58% to 91%), respectively. At 3 and 5 years, actuarial biochemical DFS was 48% (95% CI; 32% to 63%) and 34% (95% CI; 17% to 51%), respectively. Post-treatment PSA nadir was found to be a significant predictor of biochemical DFS. Actuarial biochemical DFS of patients who achieved a PSA nadir <0.5 ng/mL was 77% (95% CI; 53% to 90%) and 56% (95% CI; 25% to 78%) at 3 and 5 years, respectively. Of 49 patients, 23 (47%) achieved a post-treatment PSA nadir <0.5 ng/mL. The incidence of serious complications after salvage brachytherapy, such as incontinence and rectal, was lower than that reported after other types of salvage procedures.	2

**High Dose Rate Brachytherapy for Prostate Cancer  
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
33. Beyer DC. Permanent brachytherapy as salvage treatment for recurrent prostate cancer. <i>Urology</i> 1999; 54(5):880-883.	Observational-Tx	17 consecutive men	To determine the PSA-based freedom from second failure, survival, and morbidity of permanent brachytherapy as salvage treatment for men for whom primary EBRT of prostate cancer failed.	The 5-year actuarial freedom from second relapse was 53%. Both PSA and GS appear to be prognostic factors, although both failed to reach statistical significance. Patients with a PSA 10 ng/mL or less at the time of salvage therapy had a freedom from second relapse rate of 67% compared with 25% for men with a PSA >10 ng/mL (P=0.15). Those with low-grade tumor at the time of salvage therapy had an 83% freedom from second relapse rate compared with 30% for those with high-grade cancer (P=0.12). With 93% alive at 5 years, no significant difference was seen in survival on the basis of these prognostic groups. Acute and transient toxicity were readily managed and indistinguishable from that reported for previously unirradiated patients. Long-term complications were limited to a 24% risk of incontinence at 5 years.	2
34. Lee HK, Adams MT, Motta J. Salvage prostate brachytherapy for localized prostate cancer failure after external beam radiation therapy. <i>Brachytherapy</i> 2008; 7(1):17-21.	Observational-Tx	21 patients	To determine the toxicity and clinical outcome of salvage prostate brachytherapy for localized prostate cancer failure after EBRT.	With a median follow-up of 36 months, the actuarial 3-year and 5-year OS rates were 81% and 81%, and the biochemical failure-free survival rates were 94% and 38%, respectively. There was no significant difference in biochemical failure-free survival (P=0.98) and OS (P=0.13) for patients who had androgen ablation. Four patients developed biochemical failure and 1 patient developed distant metastasis at 59 months from treatment. Four patients had Grade 2 GU adverse events, 2 patients had Grade 1 GU adverse events, and 1 patient had a Grade 2 gastrointestinal adverse event. There were no Grade 3 or higher adverse events. All three deaths were secondary to other medical comorbidities.	2

## 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.

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Dx = Diagnostic

Tx = Treatment

## Abbreviations Key

CI = Confidence interval

CT = Computed tomography

DFS = Disease-free survival

EBRT = External-beam radiation therapy

GS = Gleason score

GU = Genitourinary

HDR = High-dose-rate

HDR-ISBT = High-dose-rate interstitial brachytherapy

HIFU = High-intensity focused ultrasound

HR = Hazard ratio

OS = Overall survival

PSA = Prostate-specific antigen

RFS = Relapse-free survival

RT = Radiation therapy