High-Risk Prostate Cancer: Local Therapy Matters

Adam L. Liss, MD, and Daniel A. Hamstra, MD, PhD

The second in a series of two articles on radiation and prostate cancer. See the May issue for the first article, "The Central Role of Radiation in Prolonging Survival for High-Risk Prostate Cancer"

Abstract

In recent years, a large focus of the management of prostate cancer has been to de-intensify treatment. Strategies to reduce treatment include decreasing the number of radiation treatment (RT) sessions, omitting surgery or RT altogether for men not expected to die of prostate cancer, and eliminating PSA screening completely. These could be effective strategies to decrease overtreatment, reduce the adverse effects of screening and treatment, and ultimately help to decrease the cost of medical care. There remains a population of men, however, who are diagnosed with more aggressive, locally advanced prostate cancer for which the standard treatment options are lacking and intensification of treatment is needed. This review summarizes treatment options for men with high-risk prostate cancer, including radical prostatectomy, external-beam radiotherapy (EBRT), and androgen-deprivation therapy (ADT). The focus here, however, will be on examining strategies to improve outcomes though intensification of local therapy using a combination of brachytherapy, EBRT, and ADT.

Key words: combination brachytherapy, high-risk prostate cancer, local control

Clinical Scenario

A 64-year-old male undergoes his first transrectal ultrasound-guided biopsy for rising PSA values over the past several years. Prior to biopsy, his PSA was 15.6 ng/mL (2 years previous, PSA was 8.1 ng/mL), though no suspicious nodularity was detected on digital rectal exam. Pathology following the prostate biopsy reveals 7 of 12 cores positive: Gleason score 4+3 in 2 cores of the right mid-gland; Gleason score 4+3 in 3 cores of the left base/apex; and Gleason score 4+4 in 2 cores of the left mid-gland/apex. He is diagnosed with Gleason 8, high-risk prostate cancer, and is interested to learn more about his treatment options.

Background

Several treatment options exist for men with prostate cancer, including radical prostatectomy (RP), external-beam radiotherapy (EBRT), androgen-deprivation therapy (ADT), and brachytherapy. Studies assessing each of these techniques as sole modality treatments have demonstrated less-than-optimal outcomes for men with high-risk disease.[1-7] Improvement in outcomes can be seen when these therapeutic approaches are combined. Radical prostatectomy followed by adjuvant EBRT has been demonstrated to provide a biochemical-free survival (bFS) benefit in 3 randomized clinical trials, and an overall survival (OS) advantage in 1 of those studies.[8-10] Robust data also have appeared within the EBRT and ADT literature, where an OS benefit with the addition of ADT to EBRT has been shown in many trials of men with high-risk prostate cancer.[5-7,11] Similarly, there has also been an OS benefit when EBRT was added to ADT.[1, 2]

Although combinations of RP plus EBRT or EBRT plus ADT have been associated with improved outcomes compared with monotherapy treatments, further improvement is needed for men with high-risk disease. Some clinicians believe that men with high-risk prostate cancer present with simultaneous local and microscopic metastatic disease at time of diagnosis, and that improved outcomes can only be achieved with better systemic treatments. Supporting this idea are newer forms of systemic therapy that include abiraterone and enzalutamide, which have demonstrated promising results in the treatment of metastatic prostate cancer, and have generated excitement for their possible use in the upfront treatment of high-risk prostate cancer.[12,13]

However, even for a man with Gleason 8 prostate cancer, as depicted in the clinical scenario here, good outcomes can be achieved with intensification of local therapy, indicating that for many men, disease remains confined to the pelvis. The strongest data for intensifying local therapy in high-risk prostate cancer come from the 3 previously mentioned randomized trials of RP plus adjuvant EBRT. That said, there is increasing evidence, including a recently reported randomized clinical trial, demonstrating that a combined approach using brachytherapy, EBRT, and ADT is associated with excellent outcomes for men with high-risk prostate cancer.[14-20] This report summarizes data on intensification of local therapy, focusing on combination EBRT and brachytherapy.

TABLE 1. Summary of Results from Prospective Randomized Studies

Study	Study Description	Number of Patients	Reported Follow-up (years)	bFS	PCSS	OS
SPCG-7/SFUO-3[1]	ADT +/- EBRT	875	10	25% vs 74%; *P* <.001	76% vs 88%; *P* <.001	61% vs 70%; *P* = .004
Intergroup[2]	ADT +/- EBRT	1205	7	N/R	79% vs 90%: *P* <.0001	66% vs 74%; *P* = .033
SWOG 8794[10]	RP +/- EBRT	431	10 (bFS); 15 (OS)	65% vs 36%; *P* <.001	N/R	48% vs 59%; *P* = .023
German ARO 96-02/AUO AP 09/95[9]	RP +/- EBRT	388	10	56% vs 35%; *P* <.001	N/R	N/R
EORTC 22911[8]	RP +/- EBRT	1005	10	39% vs 62%; *P* <.001	93% vs 95%; *P* = .341	81% vs 77%; *P* = .94
RTOG 85-31[6]	EBRT +/- indefinite ADT	977	10	9% vs 31%; *P* <.0001	78% vs 84%; *P* = .005	39% vs 49%; *P* = .002
RTOG 8610[5]	EBRT +/- 4 months ADT	456	10	20% vs 35%; *P* <.0001	64% vs 77%; *P* = .01	34% vs 43%; *P* = .12
EORTC 22863[7]	EBRT +/- 3 years ADT	415	10	N/R	70% vs 90%; *P* = .0001	40% vs 58%; *P* = .0004
RTOG 92-02[26]	EBRT + 4 vs 28 months ADT	1521	10	32% vs 48%; *P* <.0001	84% vs 89%; *P* = .004	52% vs 54%; *P* = .36
EORTC 22961[11]	EBRT + 6 vs 36 months ADT	970	5	N/R	95% vs 97%; *P* = .002	81% vs 85%; *P* = .65
MDACC[28]	70 Gy EBRT vs 78 Gy EBRT	301	8	26% vs 63%; *P* = .004	95% vs 99%; *P* = .063	78% vs 79%; *P* = .315
ASCENDE-RT[32]	EBRT + ADT vs combo + ADT	398	7	71% vs 86%; *P* = .002	94% vs 96%; *P* = .32	82% vs 86%; *P* = .29

ADT indicates androgen-deprivation therapy; bFS, biochemical-free survival; combo, combination EBRT and brachytherapy; EBRT, external-beam radiotherapy; N/R, not reported; OS, overall survival; PCSS, prostate cancer-specific survival.

Radical Prostatectomy

Although no recent prospective randomized data comparing RP to EBRT with or without ADT exist, several retrospective series have compared RP with EBRT and demonstrated largely similar results.[21-23] Important caveats to these comparisons often include the following: EBRT doses were lower than what is currently recommended; typically, there were greater numbers of patients with adverse disease characteristics in the EBRT cohorts; and a much greater rate of salvage treatment was used in the RP cohorts.[22,23] When RP alone has been used in very-high-risk prostate cancer (Gleason 9-10), there were low rates of organ-confined disease, high rates of relapse, and poor prostate cancer–specific survival (PCSS; 61% at 10 years).[24] To achieve the best results when RP is selected as the primary treatment modality for high-risk prostate cancer, EBRT for appropriately selected patients should be added to the treatment paradigm as previously discussed.[8-10]

The role of adding immediate ADT after RP for node-positive prostate cancer has been demonstrated by Messing et al,[25] although it remains somewhat controversial for most men with indications for adjuvant EBRT. The ongoing MRC/NCIC "RADICALS" trial, a 2 × 3 randomized trial assessing early versus salvage EBRT and short-term versus long-term versus no ADT, should help to address this controversy, with regard to both the need for adjuvant compared with salvage RT and to the use of androgen ablation with EBRT. **Tables 1** and **2** summarize outcomes from several studies assessing the use of RP in patients with high-risk prostate cancer.

EBRT With ADT

It is important to understand outcomes with the most widely used RT-based approach for high-risk prostate cancer, EBRT with ADT, in order to appreciate the improvement in outcomes with intensification of local therapy with combination brachytherapy. Two similarly designed randomized trials comparing ADT alone with ADT plus EBRT demonstrated improvement in multiple endpoints including PCSS: from 76% to 88% in the Widmark et al[1] study at 10 years, and from 79% to 90% in the Warde et al[2] study at 7 years. Two RTOG trials (8610[5] and 8531[6]) and

an EORTC trial[7] explored the benefit of adding ADT to EBRT. Outcomes were improved with ADT, and PCSS was demonstrated to range from 77% to 90% at 10 years.[5-7] An additional 2 studies from RTOG (92-02[26] and 94-13[27]) and 1 from EORTC[11] explored the timing and duration of ADT. Results were favorable, with PCSS reaching nearly 90% with 10 years of follow-up. These studies also demonstrated that the largest benefit of ADT when combined with definitive EBRT occurs with 2 to 3 years of use.[11,26] Unfortunately, biochemical control remained poor, with over one-half of men failing at 10 years.[26]

The aforementioned trials all used lower doses of EBRT than what is currently practiced by the majority of radiation oncologists. This is because improved biochemical control has been noted with dose-escalated EBRT. In a randomized dose-escalation trial, a significant benefit in terms of distant metastasis-free survival and bFS was noted with higher doses among the high-risk patients on study.[28] Encouraging results assessing ultra-high doses of RT, up to 86.4 Gy, have been demonstrated, though not in a randomized fashion.[29] Nonetheless, further intensification of local control is required, as nearly one-third of patients treated with ultra-high-dose EBRT had a biochemical failure at 7 years.[29] **Tables 1** and **2** summarize outcomes from several studies assessing the use of EBRT for patients with high-risk prostate cancer.

Combination Brachytherapy and EBRT

In addition to RP followed by adjuvant EBRT, an effective way to intensify local treatment is with the addition of brachytherapy in combination with EBRT. Dosimetrically, this is the most effective way to safely deliver the highest radiation dose to the prostate. Until recently, the only prospective studies comparing EBRT with combination brachytherapy and EBRT used old techniques and doses lower than what is currently employed.[30,31] Both studies showed that combination brachytherapy plus EBRT was superior to EBRT alone; however, given older EBRT technique and dose, the routine use of a brachytherapy boost was not widely embraced.[30,31] Definitive data proving the superior efficacy of combination therapy to EBRT alone comes from the recently reported ASCENDE-RT trial.[32] This prospective study randomized 398 men with intermediate-risk (31% of enrolled patients) and high-risk (69% of enrolled patients) prostate cancer to 1 year of

TABLE 2. Summary of Results from Retrospective Studies

Study	Study Description	Number of Patients	Time of Follow-up (years)	bFS	PCSS	OS
Kupelian et al[21]	EBRT >72 Gy vs combo vs RP (6% GS ≥8, 10% PSA >20)	1557	7	81% vs 77% vs 76%; *P* =.95	N/R	N/R
Zelefsky et al[23]	EBRT vs RP (EBRT cohort, 13% GS ≥8; RP cohort, 4% GS ≥8)	2380	8	N/R	95% vs 98%; *P* = .015	N/R
Boorjian et al[22]	EBRT + ADT vs RP (all high-risk, 60% of RP had EBRT after RP)	1582	10	N/R	92% vs 92%; *P* = .61	67% vs 77%; *P* <.001
Briganti et al[4]	RP (all high-risk)	1366	10	54%	91%	N/R
Ellis et al[24]	RP (all biopsy GS 9-10)	259	5 (bFS); 10 (PCSS)	37%	61%	N/R
Spratt et al[29]	86.4 Gy EBRT, 91% ADT	1002	7	68%	92%	N/R
Fang et al[17]	GS ≥8, PSA ≤15, all had LDR, 91% combo, 65% ADT	174	10	93%*	95%*	75%*
Bittner et al [14]	Very high-risk prostate cancer, 92% combo, 76% ADT	131	12	87%	87%	61%
Shilkrut et al[18]	Combo vs EBRT, 81% ADT	958	8	86% vs 60%; *P* <.0001	93% vs 87%; *P* = .003	N/R
Deutsch et al[19]	Combo vs EBRT (86.4 Gy)	630	5	93% vs 71%; *P* = .23	N/R	N/R
Taira et al[15]	LDR implant with most receiving ADT and EBRT	329	10	91%	96%	93%

* ADT subset only.
ADT indicates androgen-deprivation therapy; bFS, biochemical-free survival; combo, combination EBRT and brachytherapy; EBRT, external-beam radiotherapy; GS, Gleason score; LDR, low-dose rate; N/R, not reported; OS, overall survival; PCSS, prostate cancer-specific survival.

ADT and dose-escalated EBRT or to 1 year of ADT with combination low-dose-rate (LDR) brachytherapy and EBRT. The trial completed accrual in 2011, and results were reported in February 2015. The study reached its primary endpoint, demonstrating improved relapse-free survival (RFS) at 7 years with combination brachytherapy and EBRT compared with dose-escalated EBRT alone (86% vs 71%).[32] In the high-risk-prostate-cancer patient subset, there was an 83% versus 72% bFS benefit at 7 years and a 78% versus 58% bFS benefit with combination therapy at 9 years.[32]

Perhaps predications of the outcomes of the ASCENDE-RT trial could have been made through review of the available retrospective series. The most persuasive argument for combination brachytherapy and EBRT comes from the Prostate Cancer Results Study Group, a group created to evaluate the comparative effectiveness of prostate cancer treatments.[3] The most recent publication from the Group comprised data from over 52,000 patients, and the analysis indicated that for high-risk patients, combination brachytherapy and EBRT with or without ADT appears superior to RP or EBRT alone.[3]

The promising results from retrospective series also point to the superiority of combination versus EBRT alone for men with high-risk prostate cancer. Taira et al[15] reported outcomes for men with high-risk prostate cancer treated with an LDR brachytherapy implant combined with ADT and EBRT for most of the patients. Their excellent biochemical control rate of 91% and PCSS of 96% at 10 years compare favorably to the results from the aforementioned trials using EBRT without a brachytherapy boost. Other studies have also demonstrated excellent results with combination brachytherapy and EBRT, achieving biochemical control rates and PCSS equal to, or better than, the published data on EBRT with ADT.[14,16-20] **Tables 1** and **2** summarize outcomes from several studies assessing the use of combination brachytherapy and EBRT for patients with high-risk prostate cancer.

Local Control Matters

It should not be surprising that intensification of local therapy with combination brachytherapy is associated with improved outcomes, considering the published evidence supporting the benefits of local therapy. The first piece of evidence comes from the aforementioned 3 major trials assessing adjuvant EBRT following RP.[8-10] In all 3 studies, improved biochemical control was noted with EBRT delivered to the prostate bed after surgery. One of these trials demonstrated an OS advantage associated with the intensification of local therapy.[10]

Data from posttreatment biopsies is the second source of evidence demonstrating that combination therapy is associated with improved results. EBRT alone has been associated with rates of positive biopsy up to 65% 2 years after treatment.[33] It is important to note that the prescribed dose of RT was only 64 Gy in that series, a dose much lower than what is used today.[33] A correlation between dose and rates of positive biopsy was noted in a series by Zelefsky et al.[34] They performed posttreatment biopsies approximately 3 years after EBRT to varying radiation doses, and noted that higher doses were associated with a lower incidence of positive biopsy.[34] In the cohort of patients with high-risk prostate cancer treated with doses less than 70.2 Gy, 51% had a positive biopsy; when treated with 75.6 Gy, 33% had a positive biopsy; and when treated with doses greater than 81 Gy, 15% had a positive biopsy.[34] The high rates of positive biopsy, especially without dose-escalated EBRT, noted in the aforementioned trials are not noted in the brachytherapy literature. A recently published series assessed rates of positive posttreatment biopsies 2 years after high-dose-rate (HDR) brachytherapy (given as a single 15-Gy implant or 2 10-Gy implants, both in combination with EBRT) for men with intermediate-risk prostate cancer.[35] Only 1 of 62 men (1.6%) treated with a 15-Gy implant had a positive biopsy following combination therapy.[35] The importance of a positive biopsy after treatment has been described in a recent prospective study in which over 800 men without evidence of biochemical failure underwent a repeat prostate biopsy 2 years after EBRT. Men with recurrent or persistent disease had increased rates of biochemical and distant failure as well as worse PCSS.[36]

Finally, the third piece of evidence supporting the notion that improved local control is associated with superior outcomes appears in the ADT literature. The survival advantage seen when ADT is added to EBRT is well documented and is thought to be secondary to control of micro-metastatic disease. Data from prospective randomized trials suggest, however, that at least part of the benefit of ADT comes from improved local control. A near 50% decrease in local progression was noted in men who received 3 to 6 months of neoadjuvant ADT compared with EBRT alone in a randomized trial assessing EBRT +/- ADT.[37] Additionally, a 50% decrease in the rate of positive biopsy 2 years after EBRT and ADT was noted in a separate randomized trial assessing the role of ADT combined with EBRT for men with early, localized prostate cancer.[38] Further supporting the role of ADT and local response comes from a magnetic resonance imaging (MRI)-based response assessment study. Imaging was obtained pretreatment and 3 months following ADT, and significant reductions in all assessed MRI parameters of prostate tumors were described following ADT.[39]

Conclusion

Unfortunately, randomized trials assessing all of the different approaches to successfully treat the 64-year-old patient with high-risk prostate cancer presented here do not yet exist. What has been demonstrated from randomized clinical trials is that the best way to intensify local treatment for men following RP is to add adjuvant EBRT for appropriately selected patients, and the best way to intensify a RT regimen is to combine EBRT with

brachytherapy. Improvements such as image-guided RT (IGRT) or intensity-modulated RT (IMRT) have both resulted in improvements in RFS compared with older EBRT techniques, with only modest increases in toxicity. However, placing RT directly into the prostate has in 3 separate randomized trials proved superior to using EBRT alone for radiation dose escalation, with the most recent ASCENDE-RT trial comparing to what would be considered contemporary radiation dose and technique. Evidence from these randomized studies, in combination with a review of the available retrospective literature, strongly suggests that intensive local therapy is associated with improved outcomes. If the patient presented in the clinical scenario here were to opt for definitive RT for treatment of his high-risk prostate cancer, we would include combination brachytherapy with EBRT and ADT in our treatment discussion, as it has been associated with the best outcomes for most men with high-risk prostate cancer treated with definitive RT.

Affiliations: Adam L. Liss, MD, and Daniel A. Hamstra, MD, PhD, are from the Department of Radiation Oncology, University of Michigan, Ann Arbor.

Disclosures: Dr Liss has no relevant financial conflicts of interest to disclose. Dr Hamstra is a consultant for Augmenix, Medivation, and Myriad, and is a speaker for Varian.

Address correspondence to: Daniel A. Hamstra, MD, PhD, University of Michigan Hospital, 1500 E Medical Center Dr, UHB2C490, Ann Arbor, MI 48109. Phone: 734-936-4300; fax: 734-763-7371; email: dhamm@med.umich.edu.

REFERENCES

1. 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.

2. 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.

3. Grimm P, Billiet I, Bostwick D, et al. Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy. Results from the Prostate Cancer Results Study Group. *BJU Int.* 2012;109(suppl 1):22-29.

4. Briganti A, Joniau S, Gontero P, et al. Identifying the best candidate for radical prostatectomy among patients with high-risk prostate cancer. *Eur Urol.* 2012;61(3):584-592.

5. Roach M, 3rd, Bae K, Speight J, et al. Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: long-term results of RTOG 8610. *J Clin Oncol.* 2008;26(4):585-591.

6. Pilepich MV, Winter K, Lawton CA, et al. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma--long-term results of phase III RTOG 85-31. *Int J Radiat Oncol Biol Phys.* 2005;61(5):1285-1290.

7. Bolla M, Van Tienhoven G, Warde P, et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. *Lancet Oncol.* 2010;11(11):1066-1073.

8. Bolla M, van Poppel H, Tombal B, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). *Lancet.* 2012;380(9858):2018-2027.

9. Wiegel T, Bottke D, Steiner U, et al. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. *J Clin Oncol.* 2009;27(18):2924-2930.

10. Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. *J Urol.* 2009;181(3):956-962.

11. 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.

12. Beer TM, Tombal B. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med.* 2014;371(18):1755-1756.

13. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med.* 2013;368(2):138-148.

14. Bittner N, Merrick GS, Butler WM, et al. Long-term outcome for very high-risk prostate cancer treated primarily with a triple modality approach to include permanent interstitial brachytherapy. *Brachytherapy.* 2012;11(4):250-255.

15. Taira AV, Merrick GS, Galbreath RW, et al. Long-term outcomes of prostate cancer patients with Gleason pattern 5 treated with combined brachytherapy and external beam radiotherapy. *Brachytherapy.* 2013;12(5):408-414.

16. Wattson DA, Chen MH, Moul JW, et al. The number of high-risk factors and the risk of prostate cancer-specific mortality after brachytherapy: implications for treatment selection. *Int J Radiat Oncol Biol Phys.* 2012;82(5):e773-e779.

17. Fang LC, Merrick GS, Butler WM, et al. High-risk prostate cancer with Gleason score 8-10 and PSA level </=15 ng/mL treated with permanent interstitial brachytherapy. *Int J Radiat Oncol Biol Phys.* 2011;81(4):992-996.

18. Shilkrut M, McLaughlin PW, Merrick GS, et al. Treatment outcomes in very high-risk prostate cancer treated by dose-escalated and combined-modality radiation therapy [published online February 10, 2014]. *Am J Clin Oncol.* doi:10.1097/COC.0000000000000043

19. 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.
20. Hoffman KE, Chen MH, Moran BJ, et al. Prostate cancer-specific mortality and the extent of therapy in healthy elderly men with high-risk prostate cancer. *Cancer.* 2010;116(11):2590-2595.
21. Kupelian PA, Potters L, Khuntia D, et al. Radical prostatectomy, external beam radiotherapy <72 Gy, external beam radiotherapy > or =72 Gy, permanent seed implantation, or combined seeds/external beam radiotherapy for stage T1-T2 prostate cancer. *Int J Radiat Oncol Biol Phys.* 2004;58(1):25-33.
22. Boorjian SA, Karnes RJ, Viterbo R, et al. Long-term survival after radical prostatectomy versus external-beam radiotherapy for patients with high-risk prostate cancer. *Cancer.* 2011;117(13):2883-2891.
23. 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.
24. Ellis CL, Partin AW, Han M, Epstein JI. Adenocarcinoma of the prostate with Gleason score 9-10 on core biopsy: correlation with findings at radical prostatectomy and prognosis. *J Urol.* 2013;190(6):2068-2073.
25. Messing EM, Manola J, Sarosdy M,et al. Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. *N Engl J Med.* 1999;341(24):1781-1788.
26. 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.
27. 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.
28. 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.
29. Spratt DE, Pei X, Yamada J, et al. 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.
30. 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.
31. 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. *Radiother Oncol.* 2007;84(2):114-120.
32. Morris JW, Tyldesley S, Pai HH, et al. ASCENDE-RT: a multicenter, randomized trial of dose-escalated external beam radiation therapy (EBRT-B) versus low-dose-rate brachytherapy (LDR-B) for men with unfavorable-risk localized prostate cancer. *J Clin Oncol.* 2015;33(suppl 7; abstr 3).
33. Laverdiere J, Gomez JL, Cusan L, et al. Beneficial effect of combination hormonal therapy administered prior and following external beam radiation therapy in localized prostate cancer. *Int J Radiat Oncol Biol Phys.* 1997;37(2):247-252.
34. Zelefsky MJ, Reuter VE, Fuks Z, et al. Influence of local tumor control on distant metastases and cancer related mortality after external beam radiotherapy for prostate cancer. *J Urol.* 2008;179(4):1368-1373; discussion 1373.
35. D'Alimonte L, Helou J, Sherman C, et al. The clinical significance of persistent cancer cells on prostate biopsy after high dose-rate brachytherapy boost for intermediate-risk prostate cancer. *Brachytherapy.* 2015;14:309-314.
36. Krauss DJ, Hu C, Bahary J-P, Souhami L, et al. The importance of local control in early stage prostate cancer: outcomes of patients with a positive post-radiotherapy biopsy treated on RTOG 9408 [published online March 26, 2015]. *Int J Radiat Oncol Biol Phys.* doi:10.1016/j.ijrobp.2015.03.017.
37. 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.
38. 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.
39. Barrett T, Gill AB, Kataoka MY, et al. DCE and DW MRI in monitoring response to androgen deprivation therapy in patients with prostate cancer: a feasibility study. *Magn Reson Med.* 2012;67(3):778-785.