REVIEW

Therapeutic options for a rising PSA after radical prostatectomy

Bradley C. Carthon, MD,[1,2] David M. Marcus, MD,[2,3] Lindsey A. Herrel, MD,[4] Ashesh B. Jani, MD,[2,3,4] Peter J. Rossi, MD,[2,3,4] Daniel J. Canter, MD[2,4]

[1]Department of Hematology/Oncology, Emory University, Atlanta, Georgia, USA
[2]Winship Cancer Institute, Emory University, Atlanta, Georgia, USA
[3]Department of Radiation Oncology, Emory University, Atlanta, Georgia, USA
[4]Department of Urology, Emory University, Atlanta, Georgia, USA

CARTHON BC, MARCUS DM, HERREL LA, JANI AB, ROSSI PJ, CANTER DJ. Therapeutic options for a rising PSA after radical prostatectomy. *Can J Urol* 2013; 20(3):6748-6755.

Introduction: *Radical prostatectomy is an effective primary treatment for clinically localized prostate cancer. While many patients are cured of their disease after surgery, there are still a significant proportion of men who will develop a biochemical recurrence (BCR). In this review, we detail existing treatment algorithms for this group of patients as well as future therapies that show great promise.*

Materials and methods: *A review of the literature was performed, and relevant, high-impact articles were identified and reviewed focusing on the treatment of men with BCR after surgery for prostate cancer. Wherever possible, we used data from randomized, controlled trials. When lacking, multi-institutional retrospective studies were utilized.*

Results: *In a man with BCR, it is important to differentiate between local and distant failure to help guide treatment decision-making. In many of these men, adjuvant or salvage radiotherapy can improve local control, and in the case of salvage radiotherapy, it can improve overall survival (OS). Moreover, there are several systemic therapies available to men with gross metastases and/or castration resistant prostate cancer (CRPC) that have demonstrated a significant survival advantage as well as symptom control.*

Conclusions: *In the setting of BCR, many treatment options exist. Each modality has an effective role in the management of men with locally recurrent or metastatic prostate cancer. Furthermore, there are currently a number of effective therapies for men who progress to metastatic CRPC. In this review, we present current data detailing the role/efficacy of each therapy for a rising prostate-specific antigen (PSA) after definitive surgical therapy.*

Key Words: prostatic cancer, biochemical recurrence, salvage radiotherapy, androgen deprivation therapy, systemic therapy

Introduction

Prostate cancer is the most common male solid organ malignancy, affecting 1 in 6 men in the United States. Estimates place new prostate cancer diagnoses at over 240,000 in 2012 with over 28,000 deaths attributable to the disease each year.[1] Active surveillance, radiotherapy, and surgery all play a role in the primary treatment of prostate cancer.

Radical prostatectomy remains a primary treatment modality for patients with localized prostate cancer. Even in patients with high risk disease, a role for surgery exists as part of a multi-modal treatment plan. In the current era, robotic prostatectomy has shifted treatment patterns with a 75% increase in the number of robotic procedures performed from 2000-2008.[2]

Accepted for publication March 2013

Address correspondence to Dr. Daniel J. Canter, Department of Urology, Emory University School of Medicine, 1365 Clifton Rd. NE, Building B, Suite 1400 Atlanta, Georgia 30322 USA

Robotic surgery appears to offer reduced morbidity as compared to open prostatectomy while maintaining oncologic and functional outcomes.[3]

Depending on the patient population studied, biochemical recurrence rates after radical prostatectomy range from 15%-40%.[4-6] Current American Urological Association Prostate Guidelines define biochemical recurrence (BCR) as a prostate-specific antigen (PSA) level of ≥ 0.2 ng/mL confirmed with repeat testing.[7] BCR after prostatectomy has a variable course and survival can be prolonged. Nomograms and tools such as the Partin tables[8] enable risk stratification as well as predicting the likelihood of failure based on pre and postoperative factors. Multiple studies have demonstrated that Gleason score and PSA doubling time less than 6 months are significantly associated with risk of systemic progression of prostate cancer.[8] Similarly, data examining pre-treatment PSA velocity of > 2 ng/mL/year have demonstrated a higher risk of future mortality from prostate cancer in men treated by radical prostatectomy.[9]

In this review, we detail the available treatment options for a patient with BCR after radical prostatectomy. As new treatments emerge, the role each option plays in a multi-modal treatment strategy will continue to evolve.

Salvage radiotherapy

While radical prostatectomy very often results in long term relapse free survival, there is a subset of patients that will require postoperative radiotherapy. The best results for post-prostatectomy radiation therapy have been shown in the adjuvant setting, with three randomized trials demonstrating oncologic benefits in patients with high risk pathologic features.[10-12] Adjuvant radiotherapy is indicated if either pathologic T3 disease (including extracapsular extension or seminal vesicle invasion) or positive margins are identified at the time of surgery. While both of these factors are known to predict for PSA failure, the highest risk of local recurrence is in patients with pathologic T3 or greater disease.[13]

A prospective study performed by the European Organisation for Research and Treatment of Cancer (EORTC) randomized 1005 patients with pathologic T3 disease or positive surgical margins after prostatectomy to observation versus adjuvant radiotherapy. After a median follow up of 5 years, biochemical relapse-free survival was higher in patients who had received adjuvant radiotherapy compared to patients in the control arm (74.0% versus 52.6%, $p < 0.01$).[14] Similarly, in a multicenter prospective trial performed by the Southwestern Oncology Group (SWOG), 425 men with pathologic T3 disease were randomized to adjuvant radiotherapy versus observation.[10] After a median of 10.6 years of follow up, adjuvant radiation was found to be associated with longer median biochemical relapse-free survival compared to the control group (10.3 years versus 3.1 years, $p < 0.001$). Furthermore, while the initial analysis failed to identify improvements in rates of distant metastasis or overall survival (OS), both endpoints were found to be significantly improved in the radiotherapy arm with more extensive follow up.[11] Finally, a randomized phase III study from Germany randomized 385 patients with pathologic T3 disease to adjuvant radiation therapy versus observation.[12] In contrast to the EORTC and SWOG studies, the German study excluded all patients that did not achieve an undetectable PSA postoperatively. After 5 years, biochemical relapse-free survival was improved in the patients who had received adjuvant radiotherapy (72% versus 54%, $p = 0.0015$), with Gleason score, pre-salvage PSA, tumor stage, and margin status as significant predictors of outcome.

Alternatively, salvage radiotherapy may be given once a patient's PSA becomes detectable. Since there are no randomized trials comparing adjuvant versus salvage radiotherapy, the relative tradeoffs between the two approaches relate to potentially improved disease control with earlier treatment in the context of the estimated rates of side effects of early radiotherapy.[15] Given that the median time to distant metastasis after biochemical failure is approximately 8 years, there is a window of opportunity after the detection of recurrence in which local salvage therapy may be effective.[16] The use of radiotherapy in the salvage setting is supported by multiple high quality retrospective studies that demonstrate improved outcomes compared to controls.[17-19]

The largest series describing salvage radiotherapy is by Stephenson et al that reported the outcomes of 1540 patients with biochemical failure after radical prostatectomy who were treated with salvage radiotherapy.[17] The overall 6 year disease free survival in this study was 32%, although outcomes varied significantly according to pre-treatment disease characteristics. The pre-salvage PSA was the most important predictor of long term outcomes, with 6 year disease free survival of 48% in patients with PSA ≤ 0.50, compared to 40%, 28%, and 18% in patients with PSA 0.51-1.00, 1.01-1.50, and ≥ 1.50, respectively. Other variables found to be significantly associated with disease free survival included prostatectomy Gleason score, surgical margin status, and use of androgen deprivation therapy before or during salvage radiotherapy, and presence of lymph node metastasis.

Based on each of these variables, the authors developed a nomogram to predict long term disease free survival rates. This nomogram has been externally validated in two separate cohorts.[20,21]

In a separate study, Trock et al analyzed the outcomes of 635 patients with post-prostatectomy biochemical recurrence, including 397 who were observed, 160 who received radiotherapy alone, and 78 who received radiotherapy with concurrent androgen deprivation. With a median follow up time of 6 years after recurrence, salvage radiotherapy was associated with a 3-fold increase in prostate cancer-specific survival compared to observation. Furthermore, salvage radiotherapy was associated with significantly better overall survival compared to observation, with 10 year OS rates of 86% and 62%, respectively ($p < 0.001$). The authors found that short PSA doubling time (PSADT) was generally associated with poor outcomes. However, patients with PSADT less than 6 months also realized the most benefit from salvage radiotherapy, with 10 year prostate cancer specific survival of 82% in patients who received salvage radiation compared to 30% in patients who had been observed.[19]

The dose for salvage radiotherapy after prostatectomy typically ranges from 64 Gy to 70 Gy. While there is retrospective data suggesting a clinical benefit to higher radiation doses after prostatectomy,[22] prospective data concerning dose escalation in this setting is lacking. The target volume includes the prostate fossa and may include the pelvic lymph nodes. However, the impact of pelvic nodal radiation on biochemical and clinical outcomes is unclear and currently an active area of clinical research.

Toxicity

Long term morbidities of prostatectomy include urinary incontinence, urethral stricture, and erectile dysfunction, and these toxicities have been shown to have a measurable impact on patient-reported quality of life.[23] Importantly, postoperative radiation likely adds to these toxicities. The most robust data describing the toxicities of post-prostatectomy radiation therapy come from studies of adjuvant radiation.[10,12,14] The SWOG study, which was the only study of postoperative radiation therapy to prospectively analyze urinary incontinence, reported a significant increase in incontinence rates from 3% to 7% with adjuvant radiotherapy.[10] By contrast, an interim analysis of the EORTC study failed to demonstrate a difference in incontinence rates between treatment groups.[14] With regard to urethral stricture, the SWOG study demonstrated a higher urethral stricture rate in patients getting adjuvant radiation (17.8% in the radiation arm versus 9.5% in the observation arm, $p = 0.02$), while the German study found no significant difference between groups.[12] Finally, the impact of postoperative radiation on erectile function was evaluated in a secondary analysis of the SWOG study, which identified no significant difference in erectile dysfunction rates between patients who had received adjuvant radiotherapy and those who were observed.[10]

Systemic therapy

Patients who demonstrate a rising PSA pattern and are treatment candidates should undergo re-evaluation for local versus distant disease recurrence. Additional tests for the work up of patients with BCR include bone scan, calculation of PSA doubling time, and CT or MRI of the pelvis. The probability that a bone scan will be positive is less than 5% until the PSA reaches 40 ng/mL-45 ng/mL.[24] If men demonstrate confined local recurrence, possibilities for salvage local therapies (surgery, cryotherapy, or radiotherapy) can be considered.[25] In this setting, several studies have demonstrated that a patient's PSA doubling time correlates with the risk of clinical and systemic progression. Specifically, a PSA doubling time of 3-6 months is associated with increased prostate cancer specific mortality in patients who have undergone radical prostatectomy.[26-28] These various studies suggest that the rate of change of a patient's biochemical recurrence should be taken into consideration by clinicians when determining the need and timing of intervention.

Androgen deprivation and the development of castration resistance

The primary mode of therapy for men with metastatic prostate cancer is androgen deprivation.[29] This can be accomplished by medical or surgical castration, either alone or in combination with an antiandrogen. Antiandrogens are utilized in the setting of a significant volume of disease in order to prevent symptoms associated with the initial testosterone surge that comes from the use of gonadotropin releasing hormone (GNRH) agonists such as leuprolide or goserelin.[30] Unlike GNRH agonists, antagonists, such as degeralix, do not lead to an initial testosterone surge and are often used in the setting of high volume disease or when rapid therapeutic onset is needed. Moreover, if men show PSA progression or fail to reach castrate levels of testosterone with primary androgen deprivation, combined androgen blockade (CAB) with antiandrogens such as bicalutamide, flutamide, or nilutamide can be utilized as a secondary hormonal approach to further prevent androgen availability to cancer cells.

Inevitably, men will develop castration resistant prostate cancer (CRPC), defined as clinical signs of progression or change in PSA/imaging in the setting of castrate levels of testosterone (< 50 ng/mL). There are multiple mechanisms by which castration resistance develop, including point mutations or amplification in the androgen receptor,[31] activation of the receptor by alternate ligands,[32] activation of alternative signaling pathways such as the PI3K/AKT pathway,[33,34] and alteration of apoptotic factors or androgen receptor co-factor imbalances.[35] Once men develop castration resistance, they require additional therapies that are able to overcome these mechanisms of resistance.

Non-metastatic castration resistant disease

There is currently no FDA approved treatment that improves OS in men with a rising PSA and no signs of metastatic disease. Two separate meta-analyses have found no OS effect with CAB.[36,37] In these two studies, these agents may have an effect on PSA levels or PFS, however there was no associated OS benefit with CAB. In fact, patients may experience more adverse events and a decreased quality of life on these agents.

Of note, if men are treated with CAB for a significant amount of time (median duration in prior studies was 24-39 months) and demonstrate PSA progression, then they should undergo antiandrogen withdrawal upon PSA rise. Twenty to 40% of men with rising PSA on an antiandrogen can have a decrease in PSA levels by withdrawal of the agent.[38,39] The mechanism for this seemingly counterintuitive result may stem from alterations in the androgen receptor such that the antagonists stimulate receptor activation. Thus, removal of the antagonist can possibly prevent further activation, and an increased time of PSA suppression.

Metastatic CRPC options

Immunotherapy

Men who develop metastatic CRPC and are relatively asymptomatic are candidates for Sipuleucel-T therapy. This is an autologous vaccine based approach in which a patient's cells are harvested by leukapheresis, pulsed with peptide fragments of prostatic acid phosphatase (PAP), stimulated with granulocyte macrophage colony stimulating factor (GM-CSF), and then infused into the patient over three, biweekly cycles. This approach has demonstrated an OS benefit of 25.8 versus 21.7 months with a 22% relative risk reduction in death ($p = 0.03$) when compared to placebo.[40] Interestingly, men undergoing treatment with Sipuleucel-T must be informed that although they may not demonstrate a PSA response, they may still experience a survival benefit. Important caveats exist with the use of Sipuleucel-T: men should be relatively asymptomatic from their disease; they should not exhibit visceral metastases; they must have a good ECOG performance status (0 or 1); and, they should have a life expectancy of at least 6 months.

Docetaxel

Patients with disease that progresses rapidly as determined by a rapid PSA rise, visceral involvement, or clinical symptoms despite castrate levels of testosterone are candidates for cytotoxic chemotherapy. The Tax 327 randomized control phase III study compared mitoxantrone/prednisone to weekly docetaxel/prednisone as well as a 3 week dosing schedule of docetaxel/prednisone. Docetaxel in combination with daily prednisone given every 3 weeks led to a survival benefit of 18.9 months in the docetaxel/prednisone group versus 16.5 months in the mitoxantrone/prednisone group with a hazard ratio (HR) for death of 0.76 ($p = 0.009$).[41] In addition, patients experienced decreased pain, decreased PSA levels, and an improved quality of life when compared to the mitoxantrone/prednisone and weekly docetaxel/prednisone groups.

The SWOG 9916 study was another phase III randomized controlled trial that demonstrated an OS benefit for docetaxel based regimens. In this study, patients were randomized to receive docetaxel/estramustine or mitoxantrone/prednisone. There was an OS benefit of 17.5 months versus 15.6 months favoring the docetaxel group with an HR of 0.80 ($p = 0.02$).[42] These two trials have established docetaxel as the standard first line cytotoxic agent in men with symptomatic or rapidly progressing CRPC. To date, no other first line chemotherapeutic agent has proven to confer a survival benefit in symptomatic men.

Cabazitaxel

Cabazitaxel is a novel tubulin binding agent that was recently examined in the post-docetaxel setting. The TROPIC study was a randomized phase III study of approximately 755 patients who were randomized to receive either cabazitaxel or mitoxantrone every 3 weeks. Both groups received prednisone daily. The median OS for the cabazitaxel arm was 15.1 months compared to 12.7 months for the mitoxantrone arm (HR = 0.70, $p < 0.0001$).[43] Also, median progression-free survival was 2.8 months versus 1.4 months for the cabazotaxel patients ($p < 0.0001$). Based on this data, cabazitaxel recently received FDA approval.

Abiraterone acetate

Abiraterone acetate (AA) is a cytochrome P450 (Cyp450) 17-lyase, hydroxylase inhibitor which inhibits the conversion of cholesterol into testosterone and dihydrotestosterone (DHT). Due to its inhibition of the cholesterol biochemical pathway, AA must be given with prednisone to prevent adrenal insufficiency. The efficacy of abiraterone was demonstrated in a heavily pre-treated population of patients in the COU-AA-301 study in which almost 1200 men were randomized to receive either AA and prednisone versus placebo and prednisone. The AA cohort experienced an OS benefit of 14.8 months compared to 10.9 months (HR = 0.65, $p < 0.001$), proving its efficacy in the post-docetaxel setting.[44] The side effects of this agent included fluid retention, hypertension, and hypokalemia, all thought to be related to mineralocorticoid activity alteration.

Due to these encouraging results, AA has since been studied in chemotherapy naïve men who had evidence of progressive CRPC. In the COU-AA-302 trial, 1088 asymptomatic or mildly symptomatic men who had not received chemotherapy were randomized to receive either AA and prednisone or placebo and prednisone. In this study, there was a statistically significant difference in median PFS between the two groups: 8.3 months for placebo versus 16.5 months in the AA arm ($p < 0.0001$, HR = 0.53). Similarly, over a median follow up period of 22.2 months, there was a significant difference in median OS between the placebo and AA arms: 27.2 months as compared to a median OS not reached ($p = 0.01$, HR = 0.75). Significant differences were also observed for the secondary endpoints of time to opiate use, chemotherapy, PSA progression, and time to performance status decrease.[45] Due to these positive findings regarding AA, it has been recently approved by the FDA for use in the pre-chemotherapy setting for men with CRPC.

Enzalutamide

Enzalutamide, previously known as MDV3100, works by not only inhibiting access of androgens to the androgen receptor (AR), but it also prevents translocation of the ligand-receptor complex into the nucleus, inhibiting the association of the AR-ligand complex to DNA.[46] The recent AFFIRM Trial, a randomized controlled phase III trial of enzalutamide versus placebo in 1200 men with CRPC who had received prior chemotherapy, showed a marked improvement in median OS of 18.4 months in the study group compared to 13.6 months in the placebo group ($p < 0.001$; HR = 0.63). Statistically significant differences were also noted in all secondary endpoints including quality of life measures, time to PSA progression, time to radiographic PFS, and time to first skeletal related event.[47] Notable side effects included fatigue, diarrhea, and hot flashes. Importantly, less than 1% of patients receiving enzalutamide experienced new-onset seizures, suggesting the drug may lower a patient's seizure threshold.

Based on the results of the AFFIRM trial, enzalutamide received FDA approval for use in men with taxane-resistant CRPC. Preliminary promising data has also been obtained for enzalutamide in the chemotherapy-naïve population with 62% of men experiencing a PSA decline of > 50% in a phase I/II trial of enzalutamide.[46]

Bone health agents

Androgen deprivation therapy is a widely recognized contributor to osteoporosis. Men at high risk for bone fractures are defined by the following criteria: a 10 year risk of hip fracture > 3%, a 10 year risk of major osteoporosis related fracture > 20%, a prior hip or vertebral fracture, or those with a T-score less than or equal to -2.5 at the femoral neck or spine. Risk for fractures can be calculated using the World Health Organizations Fracture Risk Assessment Model (FRAX).[48] Patients meeting any of these criteria should receive 1200 mg of daily supplemental calcium as well as 800-1000 units of daily vitamin D.[49]

Bisphosphonates and receptor activator of nuclear factor-kappa B (RANK) ligand antagonists have important implications in preserving bone integrity. Men who received denosumab, an antibody against the RANK-ligand, had an 18% risk reduction in skeletal related events as well as a 3.6 month delay in their first skeletal-related event as compared to the bisphosphonate zoledronic acid.[50] Denosumab has also been shown to be effective in the maintenance of bone mineral density in men on ADT without gross metastases. For example, men who received denosumab every 6 months had a significant increase in bone mineral density and also had a reduced incidence of new vertebral fractures in the setting of non-metastatic prostate cancer compared to the placebo group.[51]

Promising new agents

There are intensive research efforts to identify novel pathways and agents that are active in metastatic CRPC. Radium-223 is an alpha-pharmaceutical that is well tolerated and highly focal since radium-223 is a calcium mimetic that is naturally drawn to bone metastases.[52] A phase II randomized controlled trial showed a highly favorable safety profile as well as a median OS advantage in the radium-223 group (65 versus 46 weeks in the placebo group ($p = 0.56$).[53] Moreover, there was a decrease in pain noted in 71% of treated patients.[54] Interim data from the phase III ALSYMPCA trial showed that men who received radium-223 had an overall

median survival of 14.9 months versus 11.3 months for the placebo group (HR = 0.695, p = 0.00007).[55]

Tak-700 is a CYP 450, 17,20 lyase inhibitor that has shown encouraging results in both naïve as well as previously treated patients.[56] Updated analyses have shown a response rate approaching 60%.[57] This finding has led to a pair of phase III randomized control trials of Tak-700 in men who have progressed on docetaxel-based therapy[58] as well as in men who are chemotherapy naïve.[59]

ARN-509 is a novel second generation anti-androgen that works by binding directly to the ligand binding domain of the androgen receptor, preventing translocation and DNA transcription. In recent phase II studies, there were 47 high risk non-metastatic men who were treated, and their response rate was 91%.[60] In the 46 men with metastatic disease, 25 and 21 patients respectively were treatment naïve or had prior AA. The response rate in these two groups was 88% and 29%, respectively.[61]

Cabozantinib or XL-184 is a monoclonal antibody targeting VEGF and MET receptors. This agent has shown dramatic improvement in pain control and resolution of bone lesions on bone scans in early clinical trials[62] in both taxane resistant and chemotherapy naïve patients.[63] Phase III trials are now being designed to test this agent in taxane resistant and androgen dependent men.

Conclusion

Biochemical recurrence after prostatectomy occurs in a substantial proportion of men. Whereas imaging studies can help discern distant versus local recurrence, less invasive methods such as PSA kinetics can also be helpful.[64] Adjuvant radiation therapy has demonstrated longer median biochemical relapse-free survival in patients treated with adjuvant radiotherapy compared to observation. Moreover, salvage radiotherapy has also demonstrated an overall survival benefit. From a systemic standpoint, there are currently many available agents that have shown survival benefit in metastatic CRPC. These multitudes of agents exert their effects via a variety of mechanisms to further enhance survival. It remains to be seen the magnitude of benefit/synergy from the use of these different classes of agents in combination or sequentially to help improve the outcome in men with advanced prostate cancer. □

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin* 2012;62(1):10-29.
2. Anderson CB, Penson DF, Ni S, Makarov DV, Barocas DA. Centralization of radical prostatectomy in the United States. *J Urol* 2013;189(2):500-506.
3. Tewari A, Sooriakumaran P, Bloch DA, Seshadri-Kreaden U, Hebert AE, Wiklund P. Positive surgical margin and perioperative complication rates of primary surgical treatments for prostate cancer: a systematic review and meta-analysis comparing retropubic, laparoscopic, and robotic prostatectomy. *Eur Urol* 2012;62(1):1-15.
4. Kattan MW, Eastham JA, Stapleton AM, Wheeler TM, Scardino PT. A preoperative nomogram for disease recurrence following radical prostatectomy for prostate cancer. *J Natl Cancer Inst* 1998; 90(10):766-771.
5. Han M, Partin AW, Pound CR, Epstein JI, Walsh PC. Long-term biochemical disease-free and cancer-specific survival following anatomic radical retropubic prostatectomy. The 15-year Johns Hopkins experience. *Urol Clin North Am* 2001;28(3):555-565.
6. Ward JF, Moul JW. Rising prostate-specific antigen after primary prostate cancer therapy. *Nat Clin Pract Urol* 2005;2(4): 174-182.
7. Cookson MS, Aus G, Burnett AL et al. Variation in the definition of biochemical recurrence in patients treated for localized prostate cancer: the American Urological Association Prostate Guidelines for Localized Prostate Cancer Update Panel report and recommendations for a standard in the reporting of surgical outcomes. *J Urol* 2007;177(2):540-545.
8. Boorjian SA, Tollefson MK, Thompson RH, Rangel LJ, Bergstralh EJ, Kames RJ. Natural history of biochemical recurrence after radical prostatectomy with adjuvant radiation therapy. *J Urol* 2012;188(5):1761-1766.
9. D'Amico AV, Hui-Chen M, Renshaw AA, Sussman B, Roehl KA, Catalona WJ. Identifying men diagnosed with clinically localized prostate cancer who are at high risk for death from prostate cancer. *J Urol* 2006;1766 Pt 2):S11-S15.
10. Thompson IM Jr., Tangen CM, Paradelo J et al. Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. *JAMA* 2006;296(19):2329-2335.
11. 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 follow up of a randomized clinical trial. *J Urol* 2009; 181(3):956-962.
12. 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.
13. Swanson GP, Hussey MA, Tangen CM et al. Predominant treatment failure in postprostatectomy patients is local: analysis of patterns of treatment failure in SWOG 8794. *J Clin Oncol* 2007; 25:2225-2229.
14. Bolla M, van Poppel H, Collette L et al. Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). *Lancet* 2005;366(9485):572-578.
15. Jani AB, Kao J. Postprostatectomy adjuvant versus salvage radiotherapy: a complication-adjusted number-needed-to-treat analysis. *Cancer* 2005;103(9):1833-1842.
16. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* 1999;281(17):1591-1597.
17. Stephenson AJ, Scardino PT, Eastham JA et al. Postoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. *J Clin Oncol* 2005; 23(28):7005-7012.
18. Stephenson AJ, Scardino PT, Kattan MW et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. *J Clin Oncol* 2007;25(15): 2035-2041.

19. Trock BJ, Han M, Freedland SJ et al. Prostate cancer-specific survival following salvage radiotherapy vs observation in men with biochemical recurrence after radical prostatectomy. *JAMA* 2008;299(23):2760-2769.
20. Moreira DM, Jayachandran J, Presti JC Jr et al. Validation of a nomogram to predict disease progression following salvage radiotherapy after radical prostatectomy: results from the SEARCH database. *BJU Int* 2009;104(10):1452-1456.
21. Hugen CM, Polcari AJ, Quek ML, Garza RP, Fitzgerald MP, Flanigan RC. Long-term outcomes of salvage radiotherapy for PSA-recurrent prostate cancer: validation of the Stephenson nomogram. *World J Urol* 2010;28(6):741-744.
22. King CR, Spiotto MT. Improved outcomes with higher doses for salvage radiotherapy after prostatectomy. *Int J Radiat Oncol Biol Phys* 2008;71(1):23-27.
23. 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.
24. Cher ML, Bianco FJ Jr, Lam JS et al. Limited role of radionuclide bone scintigraphy in patients with prostate specific antigen elevations after radical prostatectomy. *J Urol* 1998:160(4): 1387-1391.
25. Marcus DM, Canter DJ, Jani AB et al. Salvage therapy for locally recurrent prostate cancer after radiation. *Can J Urol* 2012;19(6): 6534-6541.
26. Roberts SG, Blute ML, Bergstralh EJ, Slezak JM, Zincke H. PSA doubling time as a predictor of clinical progression after biochemical failure following radical prostatectomy for prostate cancer. *Mayo Clin Proc* 2001;76(6):576-581.
27. Patel A, Dorey F, Franklin J, de Kernion JB. Recurrence patterns after radical retropubic prostatectomy: clinical usefulness of prostate specific antigen doubling times and log slope prostate specific antigen. *J Urol* 1997;158(4):1441-1445.
28. Zhou P, Chen MH, McLeod D, Carroll PR, Moul JW, D'Amico AV. Predictors of prostate cancer-specific mortality after radical prostatectomy or radiation therapy. *J Clin Oncol* 2005;23(28): 6992-6998.
29. Huggins C. Effect of orchiectomy and irradiation on cancer of the prostate. *Ann Surg* 1942;115(6):1192-1200.
30. Schulze H, Senge T. Influence of different types of antiandrogens on luteinizing hormone-releasing hormone analogue-induced testosterone surge in patients with metastatic carcinoma of the prostate. *J Urol* 1990;144(4):934-941.
31. Edwards J, Krishna NS, Grigor KM, Bartlett JM. Androgen receptor gene amplification and protein expression in hormone refractory prostate cancer. *Br J Cancer* 2003;89(3): 552-556.
32. Sharifi N, McPhaul MJ, Auchus RJ. "Getting from here to there"--mechanisms and limitations to the activation of the androgen receptor in castration-resistant prostate cancer. *J Investig Med* 201058(8):938-944.
33. Antonarakis ES, Carducci MA, Eisenberger MA. Novel targeted therapeutics for metastatic castration-resistant prostate cancer. *Cancer Lett* 2010;291(1):1-13.
34. Sarker D, Reid AH, Yap TA de Bono JS. Targeting the PI3K/AKT pathway for the treatment of prostate cancer. *Clin Cancer Res* 2009;15(15):4799-4805.
35. Harris WP, Mostaghel EA, Nelson PS, Montgomery B. Androgen deprivation therapy: progress in understanding mechanisms of resistance and optimizing androgen depletion. *Nat Clin Pract Urol* 2009;6(2):76-85.
36. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. Prostate Cancer Trialists' Collaborative Group. *Lancet* 2000;355(9214):1491-1498.
37. Samson DJ, Seidenfeld J, Schmitt B et al. Systematic review and meta-analysis of monotherapy compared with combined androgen blockade for patients with advanced prostate carcinoma. *Cancer* 2002;95(2):361-376.
38. Sartor AO, Tangen CM, Hussain MH et al. Antiandrogen withdrawal in castrate-refractory prostate cancer: a Southwest Oncology Group trial (SWOG 9426). *Cancer* 2008;112(11):2393-2400.
39. Scher HI, Kelly WK. Flutamide withdrawal syndrome: its impact on clinical trials in hormone-refractory prostate cancer. *J Clin Oncol* 1993;11(8):1566-1572.
40. Kantoff PW, Higano CS, Shore ND et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med* 2010;363(5):411-422.
41. Tannock IF, de Wit R, Berry WR et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004;351(15):1502-1512.
42. Petrylak DP, Tangen CM, Hussain MH et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* 2004;351(15): 1513-1520.
43. de Bono JS, Oudard S, Ozguroglu M et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet* 2010;376(9747):1147-1154.
44. de Bono JS, Logothetis CJ, Molina A et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med* 2011;364(21):1995-2005.
45. 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.
46. Scher HI, Beer TM, Higano CS et al. Antitumour activity of MDV3100 in castration-resistant prostate cancer: a phase 1-2 study. *Lancet* 2010;375(9724):1437-1446.
47. Scher HI, Fizazi K, Saad F et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med* 2012;367(13):1187-1197.
48. Saylor PJ, Smith MR. Bone health and prostate cancer. *Prostate Cancer Prostatic Dis* 2010;13(1):20-27.
49. Lekamwasam S, Adachi JD, Agnusdei D et al. A framework for the development of guidelines for the management of glucocorticoid-induced osteoporosis. *Osteoporos Int* 2012;23(9):2257-2276.
50. Fizazi K, Carducci M, Smith M et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet* 2011;377(9768):813-822.
51. Smith MR, Egerdie B, Hernandez Toriz N et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *N Engl J Med* 2009;361(8):745-755.
52. Cheetham PJ, Petrylak DP. Alpha particles as radiopharmaceuticals in the treatment of bone metastases: mechanism of action of radium-223 chloride (Alpharadin) and radiation protection. *Oncology (Williston Park)* 2012;26(4):330-337, 341.
53. Nilsson S, Franzen L, Parker C et al. Two-year survival follow-up of the randomized, double-blind, placebo-controlled phase II study of radium-223 chloride in patients with castration-resistant prostate cancer and bone metastases. *Clin Genitourin Cancer* 2013;11(1):20-26.
54. Nilsson S, Strang P, Aksnes AK et al. A randomized, dose-response, multicenter phase II study of radium-223 chloride for the palliation of painful bone metastases in patients with castration-resistant prostate cancer. *Eur J Cancer* 2012;48(5):678-686.
55. Parker C, Heinrich D, O'Sullivan JM et al. Overall survival benefit and safety profile of radium-223 chloride, a first-in-class alpha-pharmaceutical: Results from a phase III randomized trial (ALSYMPCA) in patients with castration-resistant prostate cancer (CRPC) with bone metastases. *J Clin Oncol* 2012;30, (Suppl 5): abstract 8.
56. Agus DB, Stadler WM, Shevrin DH et al. Safety, efficacy, and pharmacodynamics of the investigational agent orteronel (TAK-700) in metastatic castration-resistant prostate cancer (mCRPC): Updated data from a phase I/II study. *J Clin Oncol* 2012;30(Suppl5): abstract 98.

57. Petrylak D, Gandhi JG, Clark WC et al. A phase I/II study of safety and efficacy of orteronel (TAK-700), an oral, investigational, nonsteroidal 17,20-lyase inhibitor, with docetaxel and prednisone (DP) in metastatic castration-resistant prostate cancer (mCRPC): Updated phase II results. *J Clin Oncol* 2013;31(Suppl 6):abstract 59.
58. Dreicer R, Agus DB, Bellmunt J et al. A phase III, randomized, double-blind, multicenter trial comparing the investigational agent orteronel (TAK-700) plus prednisone (P) with placebo plus P in patients with metastatic castration-resistant prostate cancer (mCRPC) that has progressed during or following docetaxel-based therapy. *J Clin Oncol* 30, 2012 (Suppl): abstract TPS4693.
59. Saad F, Akaza H, Eisenberger MA et al. A phase III, randomized study of the investigational agent TAK-700 plus prednisone for patients with chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC). *J Clin Oncol* 29, 2011 (Suppl): abstract TPS184.
60. Smith MR, Antonarakis ES, Ryan CJ et al. ARN-509 in men with high-risk nonmetastatic castration-resistant prostate cancer (CRPC). *J Clin Oncol* 2013;31(Suppl 6):abstract 7.
61. Rathkopf DE, Antonarakis ES, Shore ND et al. ARN-509 in men with metastatic castration-resistant prostate cancer (mCRPC). *J Clin Oncol* 2013;31(Suppl 6):abstract 48.
62. Hussain M, Smith MR, Sweeney C, et al: Cabozantinib (XL184) in metastatic castration-resistant prostate cancer (mCRPC): Results from a phase II randomized discontinuation trial. *J Clin Oncol* 29, 2011; (Suppl): abstract 4516.
63. Smith MR, Sweeney C, Rathkopf DE et al. Cabozantinib (XL184) in chemotherapy-pretreated metastatic castration resistant prostate cancer (mCRPC): Results from a phase II nonrandomized expansion cohort (NRE). *J Clin Oncol* 2012;30(Suppl5):abstract 4513.
64. Wieder JA, Belldegrun AS. The utility of PSA doubling time to monitor prostate cancer recurrence. *Mayo Clin Proc* 2001;76(6):571-572.