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Clinical significance and treatment of biochemical recurrence after definitive therapy for localized prostate cancer

Wilmer B. Roberts* and Misop Han

The James Buchanan Brady Urological Institute, Johns Hopkins Medical Institutions, 600 N. Wolfe St, Marburg 1, Baltimore, MD 21205, USA

Abstract

Purpose—Radical prostatectomy and external beam radiation therapy are the established and definitive interventions for clinically localized prostate cancer. These treatment modalities are yet subject to failure observed first by biochemical recurrence, defined by increases in the serum PSA level. We investigated the significance of biochemical recurrence after definitive therapy and the available salvage therapy options for cancer recurrence.

Methods—A literature search was performed in PubMed, and applicable studies addressing biochemical recurrence and salvage options after radical prostatectomy or external beam radiation therapy were reviewed.

Results—After radical prostatectomy, a detectable serum PSA level indicates biochemical recurrence. Whether to administer salvage therapy locally or systemically depends largely on prognostic factors including PSA doubling time, Gleason's score, pathologic stage, and the time interval between radical prostatectomy and biochemical recurrence. Early initiation of salvage therapy has been shown to significantly impact on cancer outcomes.

After external beam radiation therapy, no single PSA level can define biochemical recurrence. Instead, it has been defined by increases in the PSA level above the nadir. Following radiation therapy, PSA doubling time and Gleason score play important roles in determining the need for local versus systemic salvage therapy.

Conclusions—After the diagnosis of biochemical recurrence, it is critical to perform a timely clinical assessment using the prognostic factors mentioned above. Prompt initiation of salvage therapy may prevent subsequent clinical progression and prostate cancer-specific mortality.

Keywords

Prostate cancer; Radical prostatectomy; Radiation therapy; Biochemical recurrence; PSA recurrence; Salvage

Introduction

Over the past 15 years, the prostate cancer mortality rate in the United States has gradually declined [1]. This decrement in mortality has largely been attributed to the advent of prostate-specific antigen (PSA) based screening and effective therapy for prostate cancer. Radical prostatectomy (RP) and external beam radiation therapy (EBRT) are commonly

used forms of definitive therapy for clinically localized prostate cancer. Despite advances in technique, each of the therapeutic strategies is subject to failure or biochemical recurrence (BR), as determined by subsequent rises in the serum PSA level. This article reviews the clinical significance of BR following definitive therapy for clinically localized prostate cancer. In addition, salvage options for recurrent prostate cancer are addressed.

Significance of biochemical recurrence after radical prostatectomy

If every PSA producing cell were localized to the prostate, RP would effectively abrogate PSA expression from the body. Prostate cancer, however, behaves more incipiently. It may invade the tissues locally surrounding the prostate, travel regionally to the pelvic lymph nodes, or metastasize to distant sites throughout the body. Months, even years, may pass before sufficient growth produces PSA in quantities detectable by modern assays. This re-emergence of PSA after its total abrogation is known as biochemical recurrence (BR) and typically precedes metastatic progression (MP) and prostate cancer-specific mortality (PCSM) by a median of 8 years and 13 years, respectively, following RP [2].

Not all BR is the same. Ultrasensitive assays can detect PSA in the serum down to a concentration of 0.001 ng/mL [3]. However, it is unclear at what point having a detectable PSA will affect one's survival. The growth rate of prostate cancer cells, and therefore the rate of clinical progression, is highly variable [4]. In addition, "benign" prostate tissue may potentially remain post-operatively and continue to produce PSA [5]. Therefore, BR may reflect either an insignificant process or be an early harbinger for life-threatening disease. Important questions are: (1) at what threshold level of PSA would BR represent a clinically significant threat to survival? and (2) what are the predictors of MP and PCSM in men with BR?

Following RP, BR rates up to 30% have been reported in large institutional, long-term follow up series [2,6-9]. However, not all men with BR ultimately experience PCSM. In a landmark study evaluating the natural history in men with BR (PSA $\geq$ 0.2 ng/mL) following RP, 34% developed MP at a median of 8 years from the time of BR, and 43% of the men suffered PCSM a median of 5 years after the development of metastases [2]. Similarly, Jhaveri et al. found 10-year overall survival rates of 88% versus 93% in men with or without BR following RP, respectively [10]. Therefore, they concluded that BR (PSA $\geq$ 0.2 ng/mL) did not equate to MP or PCSM.

So, what characteristics of biochemical recurrence portend a lower survival following RP? Considering that prostate cancer is generally a relatively indolent disease, death from competing causes may well overshadow PCSM. Recent studies explored the optimal definition of BR that best predicts the likelihood of MP and PCSM. Amling et al. found the highest rate of PSA progression (72%) among patients with a PSA prompt of 0.4 ng/mL, relative to 49% for a PSA prompt of 0.2 ng/mL [11]. Subsequently, Stephenson et al. found that BR defined as a PSA $\geq$ 0.4 ng/mL best explained MP [12]. Based on these studies, the PSA working group for clinical trials and outcomes reporting proposed to use the definition of BR as a PSA $\geq$ 0.4 ng/mL and subsequent increase [13]. However, using this definition of BR may artificially improve the reported recurrence-free survival outcomes following RP.

Several investigators studied the optimal PSA kinetics during BR that would predict time to MP and PCSM. In 1994, Trapasso et al. found that after BR a shorter PSA doubling time (DT) (a median of 4.3 months) most significantly correlated with MP while a longer PSA-DT (a median of 11.7 months) correlated with local recurrence or the absence of MP [14,15]. Similarly, Pound et al. found that PSA-DT less than 10 months predicted time to MP [2]. However, PSA-DT was dependent on Gleason score, and Gleason score > 7 better

predicted MP. Predictors of *time* to MP, however, were the time interval between RP and BR and advanced pathologic stage.

Subsequent studies examined PSA kinetics and other clinicopathologic parameters and their role in predicting the likelihood PCSM. For example, D'Amico et al. found that a post-operative PSA-DT of ≤ 3 months, a pre-operative PSA velocity ≥ 2 ng/mL/yr, and Gleason score ≥ 7 were highly associated with MP [16]. These aggressive clinicopathological characteristics only reflect 10–15% of clinically localized prostate cancer. Meanwhile, 43% of men with a PSA-DT ≤ 6 months will still experience MP and require subsequent therapy [17]. Interestingly, a PSA-DT < 3 months was associated with a PCSM of 31% at 5 years compared to 1% PCSM when the PSA-DT was ≥ 3 months [18].

Finally, several algorithms have been developed to determine the pattern of cancer recurrence (local versus distant) after BR [2,19,20]. One should consider the above-mentioned studies in concert with the algorithms to determine the appropriate therapy for men with BR after RP.

Salvage therapy for biochemical recurrence after radical prostatectomy

After surgical removal of the prostate, two approaches have dominated the treatment of BR, locally directed external beam radiation therapy (RT) and systemic hormonal therapy (HT). The efficacy of the therapy may largely depend on the extent of the cancer recurrence.

The rate of success of salvage RT varies significantly – between 10 and 69% [21]. Known predictors of success or failure of salvage RT include the serum PSA level at the time of RT, the presence of perineural invasion, seminal vesicle involvement [22,23], and Gleason score [21,24–27].

With the unacceptably high rates of BR and MP after salvage RT to the prostatic fossa alone, several groups investigated the effectiveness of extending the field of radiation to include the entire pelvis. When compared to a limited field (LF: prostate bed only) distribution, salvage RT to an extended field (EF: prostate fossa plus obturator nodes or greater) is associated with improvement in BRFS and overall survival, specially in those with advanced prostate cancer [28,29]. There was no significant difference in incidence of acute RT toxicity (grade 3 or higher) seen in a prospective, randomized controlled trial comparing LF versus EF [30].

At some point, however, disease may have left the pelvis, and the value of administering local therapy in that setting is in question. To evaluate the potential therapeutic benefit, Stephenson et al. performed a retrospective review of salvage EBRT in a cohort of 501 patients from 5 academic tertiary referral centers in the US, with a follow up period of 45 months. Ten percent (10%) of the men experienced MP associated with a 4% PCSM. Thus, predictors of BR and MP were as follows: Gleason score 8–10, pre-salvage PSA > 2.0 ng/mL, negative surgical margins, SVI and a PSA-DT ≤ 10 months [26]. Even in this high risk group, the progression-free probability was 22–37% – indicating that some will achieve a durable response from RT.

In a subsequent publication, the same group then developed a nomogram. Using the pre-radiation PSA, Gleason score, PSA-DT, surgical margin status, HT usage status, and presence/absence of lymph node metastases, this nomogram predicts the 6 year biochemical recurrence-free probability after salvage RT [31]. It however provides no information on the probability of metastases or PCSM.

So when is salvage RT alone insufficient? At what point should hormonal therapy (HT) be added to salvage RT? Patel et al. evaluated PSA velocity (PSAV) as a predictor of response to salvage RT alone [17]. With a median of 16 months of follow up, BRFS time was predicted to be 28 months if the PSAV was ≤ 0.035 ng/mL/month. This differed significantly from the BRFS of 16 months if the PSAV was greater than 0.035 ng/mL/month ($p = 0.0013$). Additionally, Buskirk et al. created a scoring system based on 4 risk categories using pathologic stage, Gleason score, and pre-salvage PSA [32]. Five year BRFS after RT ranged from 69% for the lowest risk group to 6% for the highest risk group. This scoring system may act as an adjunct in the decision-making process for adding HT to RT.

King et al. asked whether transient HT improves outcome or RT after RP [33]. They reported improved BRFS and overall survival in those who received RT plus 4 months of HT, compared to those who received RT alone, after RP. On multivariate analysis, if RT was given with HT in the setting of SVI, there was a significant increase in BRFS and a trend toward significantly increased overall survival. Spiotto et al. found that HT only benefited high risk patients who received RT to the entire pelvis (BRFS = 52.7%) as compared to those who received HT with RT to the prostatic bed only (BRFS = 18.2%, $p = 0.039$) [29]. Similarly, in a prospective phase III randomized controlled trial comparing whole pelvic to prostate bed only RT and neoadjuvant to adjuvant HT (RTOG 94-13), there was a trend toward improved progression-free survival and overall survival when whole pelvic RT was combined with HT [30].

Since a benefit can be observed from salvage RT after RP even in high risk patients [26], the role for monotherapy HT may be limited. In addition, there are potential side effects associated with long-term HT such as cardiovascular events [34,35]. With that in mind, medical comorbidity should be taken into account when considering long-term HT. In short, early HT may be warranted in high risk patients, but randomized controlled trials are needed to verify the benefit in the BR-only population.

Significance of biochemical recurrence after external beam radiation therapy

The definition of biochemical recurrence (BR) after external beam radiation therapy (EBRT) has changed over time in an effort to standardize results reporting and to normalize comparisons among studies. Depending on the definition used, the rates of biochemical progression differ. In 1997, the American Society for Therapeutic Radiology and Oncology (ASTRO) convened and defined BR as 3 consecutive rises in the PSA with the date of failure calculated as the midpoint between the last non-rising PSA and the first of the series defining failure [36]. Subsequently, in 2005, a consensus conference of the Radiation Therapy Oncology Group (RTOG) in concert with the ASTRO was held in Phoenix, Arizona [37]. They recommended that BR be determined by a PSA rise ≥ 2 ng/mL above the nadir, with the date of failure determined "at call". This definition (hereafter known as the "Phoenix criteria") could be used to compare BR after EBRT either with or without hormonal therapy (HT). This subsequent consensus recommended the original ASTRO definition be used only for RT delivered in the absence of HT [37].

Thames et al. assessed the performance of the ASTRO definition and other definitions of BR in predicting MP after EBRT. The authors found that the ASTRO definition performed as well or better than most of the other definitions in predicting MP. Since the differences among the definitions were not highly significant, the authors concluded a recalculation of prior publications using the ASTRO definition was not necessary [38]. Thus, using the ASTRO definition, BR rates up to 40% have been reported following EBRT [39-42].

In a long-term multi-institutional analysis of over 4800 men with clinically localized prostate cancer treated with EBRT, Kuban et al. found that progression from BR to metastasis occurred between 22 and 51% at 5 years and between 42 and 54% at 10 years according to the risk groups [41]. Interestingly, 4% of the men progressed clinically prior to meeting the definition of BR. They also found that the PSA nadir was highly associated with BR-free survival (BRFS) [41]. Meanwhile, Sandler et al. found that approximately 15% of men with BR following EBRT suffered PCSM within a median of 7 years from the date of BR [39].

In men with an increased risk of PCSM, PSA kinetics may be helpful in predicting the nature of recurrence (local versus distant/metastatic failure) as well as the time to MP and PCSM. In 1998, using a definition of BR (PSA ≥ 2 ng/mL or >1 ng/mL over the nadir PSA) similar to the Phoenix definition, Crook et al. examined PSA profiles in men whose prostates were systematically biopsied following EBRT. The authors observed a higher mean PSA nadir and shorter PSA-DT in men with distant failure compared to those with local recurrence only or no recurrence [43]. In addition, a shorter PSA-DT was associated with significantly higher risk of MP [44], PCSM [39] and lower overall survival (OS) [45] following EBRT [15]. The highest risk group to suffer PCSM was found in men with a PSA-DT < 3 months after BR from EBRT [46]. These men are likely to suffer PCSM at a median of 6 years from BR. Thus, the authors concluded that these men were most likely to harbor metastatic disease and therefore would benefit from early systemic salvage therapy.

Salvage options for biochemical recurrence after external beam radiation therapy

Several options exist for salvage of biochemical recurrence after definitive external beam radiation therapy. Because the original source of the disease, the prostate, remains in situ, many salvage therapies continue to be locally directed.

Salvage brachytherapy (BT)

The concept of treating an area with added radiation in the setting of failure of prior RT efforts relies on two assumptions (1) that the BR reflects local failure only and (2) that the disease can be eradicated by the added dose of radiation given – i.e. the disease is curable by further local therapy [47]. With biopsy-proven local recurrence of prostate cancer treated by salvage BT, long-term BRFS rates ranging from 34% to 53% have been reported [48,49]. While no pre-RT or pre-BT information was provided to determine the likelihood of occult metastatic disease, the PSA nadir (<0.5 ng/mL) after BT was a significant predictor of improved BRFS (56% at 5 years). Furthermore, while there was insufficient power to achieve significance, an association exists between salvage BT initiated at lower PSA values and improved BRFS when a PSA cut-off of 10 ng/mL is used [48]. Additionally, low grade tumors appeared to respond better than high grade tumors [48].

When HT was added in an adjuvant fashion to salvage BT for biopsy-confirmed local relapse, BRFS rates were unchanged from salvage BT alone [50]. Additionally, no difference was seen in overall survival between patients given BT alone versus BT plus HT [51]. Thus, D'Amico concluded that one should only administer salvage BT if (1) pre-PSA ≥ 10 ng/mL, (2) Gleason score ≥ 6 on biopsy, (3) clinical stage $\geq T2a$, (4) BR interval from EBRT > 1 year and (5) the absolute PSA at salvage BT < 2.0 ng/mL [47].

Salvage cryoablation

Often explored as a less invasive, outpatient alternative to salvage RP, salvage cryoablation has undergone many technical modifications in an attempt to minimize complications [52].

Whether they are indeed fewer than those incurred by experienced surgeons performing salvage RP has yet to be shown. In a study with relatively short follow up, a significant decrease in disease-free survival (DFS) was observed in men who had previously received RT + HT relative to RT-alone [53]. This implies that RT + HT refractory prostate cancer is not likely to respond to salvage cryotherapy alone as it is either more locally aggressive or metastatic at failure. Further, Gleason score and pre-cryoablation PSA had a significant effect on biochemical as well as disease-free survival following salvage cryoablation [54,55]. When divided into risk groups (low risk = PSA $\leq$ 10, Gleason score $\leq$ 6, clinical stage $\leq$ T2b versus intermediate or high risk = 1 or 2 of the following: PSA > 10, Gleason score $\geq$ 7, clinical stage > T2b), the efficacy of salvage cryotherapy was highest (BRFS = 73%) for low risk versus intermediate or high risk patients (BRFS = 45% or 11%, respectively) [56].

In an effort to describe the PSA kinetics associated with freedom from BR, Greene et al. showed that the post-cryotherapy PSA nadir (<0.5 ng/mL) was associated with freedom from BR [57]. Similarly, when the post-cryotherapy nadir was undetectable, the BRFS was longer [58]. Using PSA-DT as a predictor, a pre-cryotherapy PSA-DT $\leq$ 16 months trended toward an increased likelihood of failure of salvage cryotherapy.

Salvage prostatectomy

After definitive therapy with radiation to the pelvis, salvage RP is a technically challenging feat. This procedure, only practiced by a subset of urologists, has traditionally been fraught with complications including high rates of incontinence (44–77%), rectal injury (2–10%), and bladder neck contracture (22–41%) among others [59,60]. It has some of the longest follow up of any of the salvage procedures following definitive RT and boasts 5 year distant metastasis free survival rates of 47–83% and 10 year PCSM rates 27–36% [59,61,62].

When stratified pre-operatively to assess the likelihood of clinical progression, a post-radiation therapy PSA level < 4 ng/mL was associated with an 86% progression-free probability compared to 55% or 27% for PSAs of 4–10 ng/mL or >10 ng/mL, respectively [61]. Gleason score [59,60,62] as well as tumor DNA ploidy [60,62] was also significant predictors of PCSM on multivariate analysis. Lastly, advanced pathologic stage (SVI or positive lymph nodes) also predicts a higher likelihood of clinical disease progression [60,61], while surgical margin status significantly affects the overall BRFS. Achieving negative surgical margins at salvage RP imparted an 80% BRFS rate relative to 44% in those with positive surgical margins ($p = 0.05$) [63]. While the majority of these patients did receive neoadjuvant HT, these results nonetheless underscore the importance and value of achieving curative resection.

Summary

Following definitive therapy, once biochemical recurrence is diagnosed, it is critical to perform an early risk assessment. Successful salvage largely relies on the prompt initiation of therapy. Consideration should be given to the overall health status of the individual, as prostate cancer tends to progress relatively slowly, and each of the salvage options confer risk that may well outweigh potential benefits.

Biochemical recurrence following radical prostatectomy, as evidenced by detectable PSA, may ultimately lead to metastasis and cancer-specific mortality. Decisions regarding local versus systemic (or combined) therapy can then be made using clinicopathological predictors such as PSA-DT, Gleason score, time interval between RP and BR, and pathologic stage.

After EBRT, the definition of biochemical recurrence has largely been a moving target with consensus groups attempting to define significance based on PSA changes which are likely to reflect cancer progression. PSA-DT, PSA nadir after EBRT, and Gleason score may be used to estimate the likelihood of MP and therefore the need for systemic therapy in addition to local therapy.

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, et al. Cancer statistics, 2008. *CA Cancer J Clin*. 2008; 58:71–96. [PubMed: 18287387]
2. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA*. 1999; 281:1591–7. [PubMed: 10235151]
3. Ferguson RA, Yu H, Kalyvas M, Zammit S, Diamandis EP. Ultra-sensitive detection of prostate-specific antigen by a time-resolved immunofluorometric assay and the immulite immunochemiluminescent third-generation assay: potential applications in prostate and breast cancers. *Clin Chem*. 1996; 42:675–84. [PubMed: 8653891]
4. Simmons MN, Stephenson AJ, Klein EA. Natural history of biochemical recurrence after radical prostatectomy: risk assessment for secondary therapy. *Eur Urol*. 2007; 51:1175–84. [PubMed: 17240528]
5. Djavan B, Milani S, Fong YK. Benign positive margins after radical prostatectomy means a poor prognosis-pro. *Urology*. 2005; 65:218–20. [PubMed: 15708025]
6. Amling CL, Blute ML, Bergstralh EJ, Seay TM, Slezak J, Zincke H. Long-term hazard of progression after radical prostatectomy for clinically localized prostate cancer: continued risk of biochemical failure after 5 years. *J Urol*. 2000; 164:101–5. [PubMed: 10840432]
7. Ohori M, Goad J, Wheeler T, Eastham J, Thompson T, Scardino P. Can radical prostatectomy alter the progression of poorly differentiated prostate cancer? *J Urol*. 1994; 152:1843–9. [PubMed: 7523732]
8. Partin A, Pound C, Clemens J, Epstein J, Walsh P. Serum PSA after anatomic radical prostatectomy. The Johns Hopkins experience after 10 years. *Urol Clin North Am*. 1993; 20:713–25. [PubMed: 7505980]
9. Han M, Partin AW, Zahurak M, Piantadosi S, Epstein JI, Walsh PC. Biochemical (prostate specific antigen) recurrence probability following radical prostatectomy for clinically localized prostate cancer. *J Urol*. 2003; 169:517–23. [PubMed: 12544300]
10. Jhaveri FM, Zippe CD, Klein EA, Kupelian PA. Biochemical failure does not predict overall survival after radical prostatectomy for localized prostate cancer: 10-year results. *Urology*. 1999; 54:884–90. [PubMed: 10565752]
11. Amling C, Bergstralh E, Blute M, Slezak J, Zincke H. Defining prostate specific antigen progression after radical prostatectomy: what is the most appropriate cut point? *J Urol*. 2001; 165:1146–51. [PubMed: 11257657]
12. Stephenson AJ, Kattan MW, Eastham JA, Dotan ZA, Bianco FJ Jr, Lilja H, et al. Defining biochemical recurrence of prostate cancer after radical prostatectomy: a proposal for a standardized definition. *J Clin Oncol*. 2006; 24:3973–8. [PubMed: 16921049]
13. Scher HI, Eisenberger M, D'Amico AV, Halabi S, Small EJ, Morris M, et al. Eligibility and outcomes reporting guidelines for clinical trials for patients in the state of a rising prostate-specific antigen: recommendations from the prostate-specific antigen working group. *J Clin Oncol*. 2004; 22:537–56. [PubMed: 14752077]
14. Trapasso J, deKernion J, Smith R, Dorey F. The incidence and significance of detectable levels of serum prostate specific antigen after radical prostatectomy. *J Urol*. 1994; 152:1821–5. [PubMed: 7523728]
15. Maffezzini M, Bossi A, Collette L. Implications of prostate-specific antigen doubling time as indicator of failure after surgery or radiation therapy for prostate cancer. *Eur Urol*. 2007; 51:605–13. [PubMed: 17113217]

16. D'Amico AV, Chen M-H, Roehl KA, Catalona WJ. Identifying patients at risk for significant versus clinically insignificant postoperative prostate-specific antigen failure. *J Clin Oncol.* 2005; 23:4975–9. [PubMed: 16051949]
17. Patel R, Lepor H, Thiel RP, Taneja SS. Prostate-specific antigen velocity accurately predicts response to salvage radiotherapy in men with biochemical relapse after radical prostatectomy. *Urology.* 2005; 65:942–6. [PubMed: 15882728]
18. Zhou P, Chen M-H, 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; 23:6992–8. [PubMed: 16192586]
19. Freedland SJ, Humphreys EB, Mangold LA, Eisenberger M, Dorey FJ, Walsh PC, et al. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. *JAMA.* 2005; 294:433–9. [PubMed: 16046649]
20. Dotan ZA, Bianco FJ Jr, Rabbani F, Eastham JA, Fearn P, Scher HI, et al. Pattern of prostate-specific antigen (PSA) failure dictates the probability of a positive bone scan in patients with an increasing PSA after radical prostatectomy. *J Clin Oncol.* 2005; 23:1962–8. [PubMed: 15774789]
21. Liauw SL, Webster WS, Pistenmaa DA, Roehrborn CG. Salvage radiotherapy for biochemical failure of radical prostatectomy: a single-institution experience. *Urology.* 2003; 61:1204–10. [PubMed: 12809898]
22. Do T, Parker R, Do C, Tran L, Do L, Dolkar D. Salvage radiotherapy for biochemical and clinical failures following radical prostatectomy. *Cancer J Sci Am.* 1998; 4:324–30. [PubMed: 9815297]
23. Chawla AK, Thakral HK, Zietman AL, Shipley WU. Salvage radiotherapy after radical prostatectomy for prostate adenocarcinoma: analysis of efficacy and prognostic factors. *Urology.* 2002; 59:726–31. [PubMed: 11992848]
24. Macdonald OK, Schild SE, Vora SA, Andrews PE, Ferrigni RG, Novicki DE, et al. Salvage radiotherapy for palpable, locally recurrent prostate cancer after radical prostatectomy. *Int J Radiat Oncol Biol Phys.* 2004; 58:1530–5. [PubMed: 15050333]
25. Pacholke HD, Wajsman Z, Algood CB, Morris CG, Zlotecki RA. Postoperative adjuvant and salvage radiotherapy for prostate cancer: impact on freedom from biochemical relapse and survival. *Urology.* 2004; 64:982–6. [PubMed: 15533490]
26. Stephenson AJ, Shariat SF, Zelefsky MJ, Kattan MW, Butler EB, Teh BS, et al. Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. *JAMA.* 2004; 291:1325–32. [PubMed: 15026399]
27. Katz MS, Zelefsky MJ, Venkatraman ES, Fuks Z, Hummer A, Leibel SA. Predictors of biochemical outcome with salvage conformal radiotherapy after radical prostatectomy for prostate cancer. *J Clin Oncol.* 2003; 21:483–9. [PubMed: 12560439]
28. Kim BS, Lashkari A, Vongtama R, Lee SP, Parker RG. Effect of pelvic lymph node irradiation in salvage therapy for patients with prostate cancer with a biochemical relapse following radical prostatectomy. *Clin Genitourin Cancer.* 2004; 3:93–7.
29. Spiotto MT, Hancock SL, King CR. Radiotherapy after prostatectomy: improved biochemical relapse-free survival with whole pelvic compared with prostate bed only for high-risk patients. *Int J Radiat Oncol Biol Phys.* 2007; 69:54–61. [PubMed: 17459606]
30. Lawton CA, DeSilvio M, Roach M Iii, Uhl V, Kirsch R, Seider M, 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; 69:646–55. [PubMed: 17531401]
31. Stephenson AJ, Scardino PT, Kattan MW, Pisansky TM, Slawin KM, Klein EA, et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. *J Clin Oncol.* 2007; 25:2035–41. [PubMed: 17513807]
32. Buskirk SJ, Pisansky TM, Schild SE, Macdonald OK, Wehle MJ, Kozelsky TF, et al. Salvage radiotherapy for isolated prostate specific antigen increase after radical prostatectomy: evaluation of prognostic factors and creation of a prognostic scoring system. *J Urol.* 2006; 176:985–90. [PubMed: 16890677]

33. King CR, Presti JC, Gill H, Brooks J, Hancock SL. Radiotherapy after radical prostatectomy: does transient androgen suppression improve outcomes? *Int J Radiat Oncol Biol Phys.* 2004; 59:341–7. [PubMed: 15145146]
34. Tsai HK, D'Amico AV, Sadetsky N, Chen M-H, Carroll PR. Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. *J Natl Cancer Inst.* 2007; 99:1516–24. [PubMed: 17925537]
35. Saigal CS, Gore JL, Krupski TL, Hanley J, Schonlau M, Litwin MS. And the urologic diseases in America project. Androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer. *Cancer.* 2007; 110:1493–500. [PubMed: 17657815]
36. American Society for Therapeutic Radiology, Oncology consensus Panel. Consensus statement: guidelines for PSA following radiation therapy. *Int J Radiat Oncol Biol Phys.* 1997; 37:1035–41. [PubMed: 9169810]
37. Roach M Iii, Hanks G, Thames JH, Schellhammer P, Shipley WU, Sokol GH, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOGASTRO phoenix consensus conference. *Int J Radiat Oncol Biol Phys.* 2006; 65:965–74. [PubMed: 16798415]
38. Thames H, Kuban D, Levy L, Horwitz EM, Kupelian P, Martinez A, et al. Comparison of alternative biochemical failure definitions based on clinical outcome in 4839 prostate cancer patients treated by external beam radiotherapy between 1986 and 1995. *Int J Radiat Oncol Biol Phys.* 2003; 57:929–43. [PubMed: 14575823]
39. Sandler HM, Dunn RL, McLaughlin PW, Hayman JA, Sullivan MA, Taylor JMG. Overall survival after prostate-specific-antigen-detected recurrence following conformal radiation therapy. *Int J Radiat Oncol Biol Phys.* 2000; 48:629–33. [PubMed: 11020557]
40. Rosser CJ, Chichakli R, Levy LB, Kuban DA, Smith LG, Pisters LL. Biochemical disease-free survival in men younger than 60 years with prostate cancer treated with external beam radiation. *J Urol.* 2002; 168:536–41. [PubMed: 12131304]
41. Kuban DA, Thames HD, Levy LB, Horwitz EM, Kupelian PA, Martinez AA, et al. Long-term multi-institutional analysis of stage T1–T2 prostate cancer treated with radiotherapy in the PSA era. *Int J Radiat Oncol Biol Phys.* 2003; 57:915–28. [PubMed: 14575822]
42. Khuntia D, Reddy CA, Mahadevan A, Klein EA, Kupelian PA. Recurrence-free survival rates after external-beam radiotherapy for patients with clinical T1–T3 prostate carcinoma in the prostate-specific antigen era. *Cancer.* 2004; 100:1283–92. [PubMed: 15022298]
43. Crook JM, Choan E, Perry GA, Robertson S, Esche BA. Serum prostate-specific antigen profile following radiotherapy for prostate cancer: implications for patterns of failure and definition of cure. *Urology.* 1998; 51:566–72. [PubMed: 9586608]
44. Zagars GK, Pollack A. Kinetics of serum prostate-specific antigen after external beam radiation for clinically localized prostate cancer. *Radiother Oncol.* 1997; 44:213–21. [PubMed: 9380819]
45. Lee AK, Levy LB, Cheung R, Kuban D. Prostate-specific antigen doubling time predicts clinical outcome and survival in prostate cancer patients treated with combined radiation and hormone therapy. *Int J Radiat Oncol Biol Phys.* 2005; 63:456–62. [PubMed: 15927415]
46. D'Amico AV, Moul JW, Carroll PR, Sun L, Lubeck D, Chen M-H. Surrogate end point for prostate cancer-specific mortality after radical prostatectomy or radiation therapy. *J Natl Cancer Inst.* 2003; 95:1376–83. [PubMed: 13130113]
47. D'Amico AV. Analysis of the clinical utility of the use of salvage brachytherapy in patients who have a rising PSA after definitive external beam radiation therapy. *Urology.* 1999; 54:201–3. [PubMed: 10443710]
48. Beyer DC. Permanent brachytherapy as salvage treatment for recurrent prostate cancer. *Urology.* 1999; 54:880–3. [PubMed: 10565751]
49. Grado GL, Collins JM, Kriegshauser JS, Balch CS, Grado MM, Swanson GP, et al. Salvage brachytherapy for localized prostate cancer after radiotherapy failure. *Urology.* 1999; 53:2–10. [PubMed: 9886580]
50. Wong WW, Buskirk SJ, Schild SE, Prussak KA, Davis BJ. Combined prostate brachytherapy and short-term androgen deprivation therapy as salvage therapy for locally recurrent prostate cancer after external beam irradiation. *J Urol.* 2006; 176:2020–4. [PubMed: 17070243]

51. Lee HK, Adams MT, Motta J. Salvage prostate brachytherapy for localized prostate cancer failure after external beam radiation therapy. *Brachytherapy*. 2008; 7:17–21. [PubMed: 18201939]
52. Bong G, Keane T. Salvage options for biochemical recurrence after primary therapy for prostate cancer. *Can J Urol*. 2007; 14:2–9. [PubMed: 18163938]
53. Pisters LL, Perrotte P, Scott SM, Greene GF, von Eschenbach AC. Patient selection for salvage cryotherapy for locally recurrent prostate cancer after radiation therapy. *J Clin Oncol*. 1999; 17:2514. [PubMed: 10561317]
54. Izawa JI, Madsen LT, Scott SM, Tran J-P, McGuire EJ, von Eschenbach AC, et al. Salvage cryotherapy for recurrent prostate cancer after radiotherapy: variables affecting patient outcome. *J Clin Oncol*. 2002; 20:2664–71. [PubMed: 12039928]
55. Ng CK, Moussa M, Downey DB, Chin JL. Salvage cryoablation of the prostate: followup and analysis of predictive factors for outcome. *J Urol*. 2007; 178:1253–7. [PubMed: 17698104]
56. Ismail M, Ahmed S, Kastner C, Davies J. Salvage cryotherapy for recurrent prostate cancer after radiation failure: a prospective case series of the first 100 patients. *BJU Int*. 2007; 100:760–4. [PubMed: 17662081]
57. Greene GF, Pisters LL, Scott SM, Von Eschenbach AC. Predictive value of prostate specific antigen nadir after salvage cryotherapy. *J Urol*. 1998; 160:86–90. [PubMed: 9628611]
58. de la Taille A, Hayek O, Benson MC, Bagiella E, Olsson CA, Fatal M, et al. Salvage cryotherapy for recurrent prostate cancer after radiation therapy: the Columbia experience. *Urology*. 2000; 55:79–84. [PubMed: 10654899]
59. Sanderson KM, Penson DF, Cai J, Groshen S, Stein JP, Lieskovsky G, et al. Salvage radical prostatectomy: quality of life outcomes and long-term oncological control of radiorecurrent prostate cancer. *J Urol*. 2006; 176:2025–32. [PubMed: 17070244]
60. Ward JF, Sebo TJ, Blute ML, Zincke H. Salvage surgery for radiorecurrent prostate cancer: contemporary outcomes. *J Urol*. 2005; 173:1156–60. [PubMed: 15758726]
61. Bianco JFJ, Scardino PT, Stephenson AJ, DiBlasio CJ, Fearn PA, Eastham JA. Long-term oncologic results of salvage radical prostatectomy for locally recurrent prostate cancer after radiotherapy. *Int J Radiat Oncol Biol Phys*. 2005; 62:448–53. [PubMed: 15890586]
62. Liang C, Sebo TJ, Slezak J, Pisansky TM, Bergstralh EJ, Neumann RM, et al. Predictors of survival for prostate carcinoma patients treated with salvage radical prostatectomy after radiation therapy. *Cancer*. 1998; 83:2164–71. [PubMed: 9827721]
63. Garzotto M, Wajsman ZEV. Androgen deprivation with salvage surgery for radiorecurrent prostate cancer: results at 5-year followup. *J Urol*. 1998; 159:950–5. [PubMed: 9474190]