Management of Asymptomatic Rising PSA After Prostatectomy or Radiation Therapy

ABSTRACT: Controversy exists over the optimal management of patients with an asymptomatic rising prostate-specific antigen (PSA) following definitive therapy for clinically localized prostate adenocarcinoma. Post-prostatectomy patients whose residual disease is felt to be confined to the area immediately adjacent to the prostatic bed may benefit from external-beam radiation therapy. Systemic recurrence may be managed with either watchful waiting or treated with hormone deprivation. Post-radiation therapy patients felt to have local disease progression may undergo salvage radical prostatectomy (if disease is clinically confined to the prostate gland) or cryotherapy (although this is still considered “experimental”). Patients who are not candidates for salvage therapy can be managed with watchful waiting or hormone deprivation. For patients in whom definitive therapy has failed, treatment should be individualized according to pathologic stage (if post-prostatectomy), rate of PSA progression, surgical candidacy status (if post-radiation therapy), and attitudes and expectations of the physician and patient. [ONCOLOGY 11(4):457-465, 1997]

Introduction

A denocarcinoma of the prostate is the most common malignancy in men and the second most common cause of cancer deaths in North American males.[1,2] Definitive therapy for clinically-localized adenocarcinoma of the prostate (stages T1 and T2) is either radical prostatectomy or radiation therapy. Prostate-specific antigen (PSA) was first described by Wang et al in 1979.[3] Prostate-specific antigen has enzymatic activity and is produced by the prostate and periurethral glands in men.[4] Following radical prostatectomy, serum PSA should decrease to an undetectable level if all prostatic tissue has been removed. Several investigators have described the relationship between postoperative PSA and the subsequent risk of disease recurrence.[5,6]

Rising PSA Post-Prostatectomy

Post-prostatectomy PSA is a sensitive indicator of disease, and its elevation often precedes clinically-recurrent disease by months to years.[7] Pathologic stage has been shown to correlate with the risk of residual disease, progression, and survival.[8-10] In some series, as many as 50% of patients undergoing radical prostatectomy have been found to have extracapsular extension on final pathologic staging. Not all tumors that are pathologic stage T3 have the same risk of local recurrence and/or progression. Among patients found to be margin-positive by pathologic staging, Coetzee et al have suggested a difference in local disease recurrence between patients whose PSA drops to an undetectable level postoperatively and those whose PSA does not become undetectable.[11] They feel that patients who are margin-positive (C2) but who attain an undetectable PSA postoperatively, followed by a delayed increase in PSA, have possibly only a local recurrence in the prostatic fossa, whereas patients whose PSA does not fall to undetectable levels postoperatively most likely have microscopic metastases. In addition to PSA and digital rectal examination, transrectal ultrasound is useful in detecting local recurrence following radical prostatectomy.[12] Prostate-specific antigen failure rates following...
radical prostatectomy for pathologically organ-confined disease range from 9% to 14%.\[5,13,14\] Upon review of these results, several investigators have found the presence of unconfined disease that was overlooked by histopathologic examination.\[14-16\]

**Adjuvant Radiation Therapy**

The primary question to be addressed is whether PSA failure following radical prostatectomy represents local recurrence, and thus, is amenable to treatment with adjuvant radiation therapy. Klein has concluded that PSA failure patients post-prostatectomy who have low Gleason grade, low initial PSA, and low PSA velocity after surgery, are more likely to benefit from adjuvant radiation. He also found that such patients who have negative margins are likely to have metastatic disease.\[17\] Several studies have shown a poor long-term response to adjuvant radiation in patients who never achieve undetectable PSA levels following radical prostatectomy.\[9,18\] Studies that support the use of adjuvant radiation therapy for PSA failure cite improved local control of disease and up to 53% success in reaching undetectable PSA levels; however, this does not translate into an improvement in the incidence of distant metastasis or overall survival.\[19-21\]

The timing of salvage radiation following PSA failure has also been investigated. The potential cure rate after waiting for the PSA level to rise before initiating salvage radiation is £ 33%.\[22\] Serum PSA concentrations are reduced to the undetectable range in 30% to 80% of men treated with salvage radiation therapy. However, in 30% to 60% of men who respond to radiation therapy, the serum PSA concentration will rise again within 2 years.\[23\]

New methods to help determine local vs distant recurrence include reverse-transcriptase polymerase chain reaction (PCR) and Prosta-scint (a monoclonal antibody to cell membrane PSA).\[24\]

**Androgen Deprivation Therapy**

Data suggest that patients whose PSA fails to normalize initially after radical prostatectomy are likely to have distant metastases, whereas those who develop a delayed (more than 18 months) rise in PSA are likely to have a local recurrence.\[25\] Watchful waiting is one option for the management of patients with PSA failure following radical prostatectomy who are not felt to have a local recurrence. The decision as to when such a patient would benefit from androgen-deprivation therapy remains controversial. The mainstay of therapy for advanced metastatic prostate cancer has been either bilateral scrotal orchiectomy, estrogen therapy, or androgen blockade. However, in the last 5 years, the definition and treatment of "advanced prostate cancer" have undergone a metamorphosis. Advanced adenocarcinoma of the prostate now not only includes stage D2 (M1 disease) but also an increasing PSA level after radical prostatectomy or other definitive local therapy.\[FIGURE 1\]

![Progression-Free Survival](image1)

**FIGURE 2**

![Same Subset, Overall Survival](image2)

It has been established that a substantial survival benefit is enjoyed by those with minimal metastatic disease who are treated with combined androgen blockade.\[reference 26 and Figure1\]
and Figure 2] Androgen deprivation therapy decreases PSA levels initially in nearly all men. Among men with stage D2 disease, only 9% still have undetectable serum PSA levels after 2 years. Also, 72% of men who have a good initial response (within the first 6 months) experience increases in serum PSA within the second 6 months following therapy.[27]

**Novel Therapeutic Approaches**

Some patients whose PSA rises after definitive local therapy (with radical prostatectomy, radiation therapy, or cryotherapy) and their physicians are apprehensive about using standard androgen deprivation therapy. In such patients, novel therapeutic approaches have been investigated. In several studies, Fleshner and Trachtenberg have shown durable decreases in PSA levels using the combination of finasteride (Proscar) and flutamide (Eulexin) in patients with advanced prostate cancer.[28] It is not known whether this combination will affect time to progression or overall outcome in these patients.

**Summary**

In summary, a PSA that does not fall to an undetectable level following radical prostatectomy has been associated with metastatic disease, whereas a PSA level that initially drops to an undetectable level and later begins rising is possibly associated with local recurrence. Patients whose PSA does not fall to an undetectable level following radical prostatectomy are unlikely to be cured by adjuvant radiation therapy. Patients whose PSA nadir is undetectable following radical prostatectomy and then subsequently becomes detectable should undergo restaging. If, after restaging, these patients are felt to have local recurrence, they may benefit from adjuvant radiation therapy.

Controversy exists over the efficacy of early vs delayed hormonal therapy for an asymptomatic rising PSA following radical prostatectomy. Combined androgen therapy has shown both increased time to progression and survival when compared with bilateral orchiectomy or a luteinizing hormone-releasing hormone (LHRH) agonist alone.

Finally, novel therapies have been proposed to lower PSA while decreasing side effects usually associated with standard androgen deprivation therapy. However, a survival advantage of such therapies has yet to be demonstrated.

**Rising PSA Post- Radiation Therapy**

Prostate-specific antigen has proven to be the optimal means of monitoring disease status after radiation therapy for clinically-localized adenocarcinoma of the prostate. Although an undetectable serum PSA following radical prostatectomy is the most sensitive measure of disease-free status, it does not always hold true that PSA falls to undetectable levels after radiation therapy.

There are varying opinions as to the PSA nadir or baseline PSA following radiation therapy that represents disease-free status. Prostatic epithelium that remains following radiotherapy, whether it is external-beam radiation or interstitial implantation, continues to secrete a measurable baseline level of PSA.[29] Although a positive biopsy following radiotherapy does not always indicate progressive disease, it does identify a group of patients who are more likely to experience disease progression when compared with those with a negative post-irradiation biopsy.[30,31] Some investigators have advocated the PSA doubling time as an indicator of disease progression, whereas others concentrate on PSA nadir.[32-34] It is important to clarify whether a stable baseline PSA post-treatment or an undetectable PSA is representative of disease-free status.

Several prognostic factors have been identified that correlate strongly with PSA relapse following radiotherapy. These include clinical stage, Gleason score, and pretreatment PSA.[35-37]

**Salvage Radical Prostatectomy**

Other researchers have shown the prognostic importance of post-treatment PSA in predicting disease-free progression.[38-40] It is important to differentiate between local vs regional metastatic recurrence of prostate cancer following definitive radiotherapy. Only in those patients who are felt to have truly local recurrent disease is salvage radical prostatectomy indicated. The definition of local recurrence after radiotherapy is a positive needle biopsy in conjunction with an increasing PSA level in a patient with no evidence of distant metastases.[41] Patients being considered for salvage radical prostatectomy should not only meet the risk requirement for local recurrence but also should be appropriately healthy for this operation, with a life expectancy of 10 years or more.

In patients whose cancer is confined to the prostate gland (stage T1 or T2), the results of salvage prostatectomy have been good. Disease-free survival rates, as determined by an undetectable PSA,
have ranged from 52% to 82%.\[41,42\] Pathologic upstaging is common in this group, with approximately 70% of the specimens showing capsular penetration (T3) and nearly 60% exhibiting positive surgical margins.\[41-44\]

In addition, salvage prostatectomy is technically challenging. The rate of complications is significant. These include rectal injury, anastomotic strictures, and the possible need for cystoprostatectomy due to locally-advanced disease.\[41,44\] Patients who undergo salvage prostatectomy after prior irradiation also have a higher incidence of post-prostatectomy incontinence due to the combined effects of the two therapies.\[41-44\]

**Cryosurgical Ablation**

Thanks to technological improvements in ultrasonic guidance and the advent of percutaneous access techniques and urethral warming, cryosurgical ablation of the prostate has received renewed interest over the last 6 years. Long-term data on disease-free survival after cryoablation therapy are not yet available.

Several centers have attempted to show the efficacy of cryoablation therapy in patients in whom radiation therapy fails (as evidenced by a rising PSA). Cryotherapy appears to lower PSA dramatically in most of these patients. However, results are confounded by the addition of androgen deprivation therapy in many patients and the limited number of patients studied. In two groups of patients treated with cryoablation following radiation failure, PSA dropped to less than 0.4 ng/mL in 30% and 36%, respectively. Complications were frequent and significant, with urethral sloughing occurring in 15% to 50% and incontinence in 10% to 95%.\[45-47\]

**Androgen Deprivation Therapy**

**REFERENCE GUIDE**

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A rising PSA following definitive radiotherapy is evidence of disease recurrence and/or progression. Depending on the situation, a rising PSA following radiation therapy may prompt either imaging studies to detect metastases and/or prostate biopsies. In most patients who are not surgical candidates or who have advanced local or metastatic disease, observation or androgen deprivation therapy may be indicated.

As mentioned above, early vs delayed hormonal manipulation is controversial. If watchful waiting is elected, the PSA level can be monitored. The patient can then be treated with hormone manipulation if the PSA doubling time accelerates or if the patient develops metastatic disease (as evidenced by a positive bone scan) or becomes symptomatic either due to local progression (bladder outlet or ureteral obstruction) or bone pain secondary to metastases. If early androgen deprivation therapy is chosen, one can use either monotherapy with bilateral orchiectomy or an LHRH agonist or combined androgen blockade. Novel agents, such as finasteride and flutamide, also have been shown to lower PSA in this subset of patients with fewer side effects than standard therapy.\[26,28\]

**Conclusions**

Serum PSA should become undetectable following radical prostatectomy for clinically-localized adenocarcinoma of the prostate, and should become either undetectable or achieve a low continuous baseline level following radiotherapy. Approximately 23% of men will experience a PSA failure at 10 years following radical prostatectomy. Also, approximately 38% of men will experience
an increase in PSA levels following radiation therapy at 3 years' follow-up.[48]
Thus, an asymptomatic rise in PSA following therapy with either radical prostatectomy or radiation therapy, should be carefully assessed. A rising PSA following either form of definitive therapy is an indication of disease recurrence and/or progression. The important question to be answered is whether the recurrence is local, regional, or metastatic. Therapeutic options must be considered on an individual basis, depending on the probability that the recurrence is local or metastatic.
In certain instances, local recurrence may be treatable with adjuvant therapy. It should be stressed that patients who have undergone potentially curative radical prostatectomy or radiation therapy are at much higher risk for complications from salvage therapy. Cure rates are also exceptionally low in the groups undergoing salvage treatment.
Hormone therapy is effective in lowering PSA values in these groups. However, it is uncertain whether early therapy affords a survival advantage over delayed therapy. In patients with metastatic disease, several studies have shown an advantage of combined androgen blockade over monotherapy with regard to time to progression and survival.
Patients with an asymptomatic rising PSA following radical prostatectomy or radiotherapy remain a challenge. Further improvements in pretreatment staging and technological advances will hopefully decrease the incidence of an asymptomatic rising PSA in the future.

References:


