

# Current Controversies in the Management of Biochemical Failure in Prostate Cancer

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**Abstract:** Approximately 35% of prostate cancer patients will experience a biochemical recurrence within 10 years of receiving treatment. Among patients who develop biochemical recurrence, approximately one-third will develop radiographic evidence of metastatic disease within 8 years from the time of prostate-specific antigen (PSA) elevation. Development of biochemical recurrence with a rising PSA level causes significant anxiety for both the patient and his treating oncologist. There is no consensus regarding the PSA level that indicates disease recurrence after radical prostatectomy. Androgen-deprivation therapy (ADT) is the standard of care for these patients. The key components that influence the consideration of ADT are the rate of change of the PSA level (PSA doubling time), the patient's anxiety regarding his PSA level, and the side effects associated with ADT. One of the most prominent controversies in the treatment of biochemical recurrence is the timing of ADT (early vs late) for treatment of PSA recurrence. An emerging treatment option is continued active surveillance, especially in patients who are asymptomatic. Other management approaches under investigation include intermittent ADT, the combination of ADT and novel agents, and peripheral androgen blockade.

Each year in the United States, approximately 240,890 men are diagnosed with prostate cancer, and approximately 33,720 men die from the disease.<sup>1</sup> Initial therapy for clinically localized prostate cancer can include active surveillance, radical prostatectomy, or radiotherapy. Definitive treatment of prostate cancer using prostatectomy or radiation therapy, with their known potential side effects, often results in cure.

Patients who undergo definitive treatment with a radical prostatectomy typically are quoted 5- and 10-year biochemical progression-free survival (PFS) rates of 80% and 68%, respectively.<sup>2</sup> Radiotherapy, consisting of either external beam radiation therapy or brachytherapy, can also be utilized for definitive therapy of clinically localized prostate cancer, with a 10-year biochemical PFS of 50–70%.<sup>3</sup> Despite high cure rates with definitive therapy, approximately 35% of patients will still experience a biochemical recurrence within 10 years of receiving treatment.<sup>2</sup> Among patients who develop biochemical recurrence, approximately one-third will develop radiographic evidence of

## Keywords

Prostate cancer, biochemical recurrence, prostate-specific antigen, androgen-deprivation therapy

metastatic disease within 8 years from the time of prostate-specific antigen (PSA) elevation.<sup>4</sup>

Development of biochemical recurrence with a rising PSA level causes significant anxiety for both the patient and his treating oncologist. It is widely acknowledged that the typical patient with prostate cancer is older than 60 years, and he may have other medical comorbidities as competing causes for overall mortality.<sup>3,5</sup> In fact, up to 18% of patients with a biochemical recurrence die from causes other than prostate cancer.<sup>5</sup> Thus, the treating oncologist must balance a patient's competing comorbidities, anxiety level, and overall risk of developing metastatic disease to determine whether prostate cancer may be the ultimate cause of death.

### Definition of Biochemical Recurrence

One issue that causes anxiety in patients is the absolute value of the PSA level. It is important to note that after a radical prostatectomy, the PSA is expected to fall to undetectable levels because the source of PSA production is, presumably, removed. Thus, patients with detectable PSA levels after a prostatectomy are thought to have biochemical recurrence due to the presence of residual benign prostate tissue or prostate cancer.<sup>6</sup> However, there is no consensus opinion regarding the PSA level that indicates disease recurrence after radical prostatectomy. The American Urological Association (AUA) updated its guidelines in 2006 in order to better establish standards for data reporting and comparison of patients who undergo radical prostatectomies. The AUA acknowledged that there is large variability in defining biochemical recurrence based on a specific PSA level, but it suggested that a level between 0.2 ng/mL and 0.4 ng/mL appears to be the best predictive marker of early treatment failure.<sup>7,8</sup>

For patients who receive definitive radiation therapy, the Radiation Therapy Oncology Group–American Society for Therapeutic Radiology and Oncology (RTOG-ASTRO) consensus has defined biochemical failure as a PSA rise of 2 ng/mL or more above the nadir PSA.<sup>4,9</sup> The ASTRO criteria have been criticized because the time interval between consecutive increases was not specified, and there is a need to backdate the time of failure. However, it is important to note that in spite of these shortcomings, the ASTRO criteria allow for comparisons among patients.

Because patients with prostate cancer are now sensitized to the value of the PSA level, it is important to explain to them the criteria by which biochemical recurrence is defined. For example, it is important to counsel patients who undergo prostatectomies that although an undetectable PSA level is preferred, a detectable PSA level is not necessarily a predictor of treatment failure.

Likewise, in a patient with a PSA nadir of 0.75 ng/mL after radiation therapy, the PSA level would need to rise above 2.75 ng/mL in order to meet the criteria for biochemical recurrence. Many patients understandably become anxious about any change in their PSA level, but it is important to explain that PSA levels can fluctuate over time and there is a large variability in defining biochemical recurrence.

### Localized Therapy: Adjuvant and Salvage Therapy

After a radical prostatectomy, adjuvant radiation therapy (administered within 16 weeks after surgery) offers an improvement in the 10-year biochemical PFS (36% vs 12% in observation alone).<sup>10</sup> This option may benefit men at high risk for local recurrence and with pathologic features, including positive surgical margins, seminal vesicle involvement, or extracapsular extension.<sup>10-12</sup> The SWOG 8749 trial determined that there was no statistically significant improvement in metastasis-free survival or overall survival in men who received adjuvant radiation therapy as compared with men who underwent observation.<sup>12</sup> Metastasis-free survival was 14.7 years in the treatment arm and 13.2 years in the observation arm (hazard ratio, 0.75; 95% confidence interval, 0.55–1.02;  $P=.06$ ).<sup>12</sup> Importantly, men receiving adjuvant radiation therapy experienced more adverse events, such as rectal bleeding, urethral strictures, and total urinary incontinence. It has been acknowledged that this study may not have detected a difference between the arms for 2 reasons: the sample size may have been too small, and approximately one-third of the patients in the observation arm eventually received pelvic radiotherapy. Thus, it can also be argued that deferred radiation therapy is a reasonable approach.

The European Organisation for Research and Treatment of Cancer (EORTC) 22911 trial evaluated patients with at least 1 of the following: extraprostatic extension, positive surgical margins, or invasion of the seminal vesicles. Patients were randomized to adjuvant radiation therapy or a wait-and-see approach until local failure. Patients who received immediate adjuvant radiation therapy had a significant improvement in their 5-year biochemical PFS (74% vs 52%).<sup>13</sup> A third randomized controlled trial, ARO 96-02/AUO AP 09/95 (Arbeitsgemeinschaften Radiologische Onkologie und Urologische Onkologie der Deutschen Krebsgesellschaft), evaluated patients with pathologic stage T3 prostate cancer and an undetectable postoperative PSA level. Patients with high-risk features had a significant reduction in 5-year biochemical PFS (72% vs 54%), thus supporting both the SWOG and EORTC trials.<sup>14</sup>

Salvage radiation therapy offers a 62–84% probability of PSA control at 5 years, after the development of biochemical recurrence. The SWOG 8749 trial acknowledged that the impact of a reduced risk of PSA relapse after radiotherapy is unknown, and with the lack of significant difference in overall survival between the adjuvant and observation arms, the known complications associated with radiation therapy are that much more important to consider when making decisions regarding adjuvant radiation therapy.<sup>12</sup> For patients with high-risk features after prostatectomy, it is worthwhile to seek a consultation with a radiation oncologist to discuss the risks and benefits of adjuvant radiotherapy as compared to salvage radiotherapy.

For patients who receive primary radiation therapy, treatment options include continued active surveillance or salvage prostatectomy. Salvage prostatectomy is not widely accepted as a therapy for biochemical recurrence due to the associated risks with surgical intervention. Typically, patients who undergo initial radiotherapy for treatment of their prostate cancer are more likely to have medical comorbidities that preclude a prostatectomy. In a literature review spanning 1980–2011, Chade and colleagues analyzed 40 studies evaluating salvage radical prostatectomy as a treatment option for patients with biochemical recurrence. Patients undergoing salvage prostatectomy had a 5-year and 10-year biochemical progression-free probability of 66% and 34%, respectively, with a cancer-specific survival of 70%.<sup>15,16</sup> A separate retrospective analysis confirmed a 5- and 10-year biochemical recurrence-free probability of 48% and 37%, respectively.<sup>17</sup> The risks of urinary and sexual dysfunction were high, with approximately 80% of patients requiring intervention for sexual dysfunction.<sup>15</sup> Patients must be carefully selected to undergo this procedure because of the potential for higher surgical morbidity, including urinary and sexual dysfunction.

Salvage brachytherapy is a potential treatment option after definitive radiation therapy for carefully selected patients because it is less invasive than prostatectomy, yet can potentially offer curative treatment. The majority of studies evaluating salvage brachytherapy do so after radiotherapy, with 5-year biochemical disease-free survival rates ranging from 20–87%.<sup>18–23</sup> There is experience at our institution employing salvage brachytherapy in 12 patients, with a 4-year biochemical disease-free survival of 63% and overall survival of 54%.<sup>24</sup> The most common complications were genitourinary or gastrointestinal toxicities, such as erectile dysfunction, urinary frequency, urinary obstruction, urgency, dysuria, or diarrhea. Although the optimal dose of radiation is still being evaluated, and patients must be carefully selected for this procedure, salvage brachytherapy is a potential treatment option.

Salvage cryotherapy has been evaluated in several trials, with a 5-year biochemical control rate of approximately 50%. However, the procedure entails significant risks, such as urinary incontinence, urinary obstruction, and significant rectal pain, as well as rectourethral fistula formation.<sup>24–29</sup> However, cryotherapy is more likely to fail in patients with a PSA level at or greater than 10 ng/mL, a Gleason score of 9 or 10, or a pre-radiation therapy clinical stage greater than T2.<sup>30</sup> Although this therapy has not been directly compared with other salvage treatments, it is recognized that patient selection is important to achieve results.

### Systemic Therapy for Biochemical Recurrence

One of the most prominent controversies in the treatment of biochemical recurrence is the timing of androgen-deprivation therapy (ADT; early vs late) for treatment of PSA recurrence because findings from clinical trials are mixed. Although ADT is considered the standard of care, an emerging and acceptable treatment option is continued active surveillance, especially in patients who are asymptomatic.

The Veterans Administration Co-operative Urological Research Group (VACURG) published several studies that evaluated patients with advanced prostate cancer in order to determine the optimal timing of androgen suppression (early vs late). Although there was a suggestion that early androgen suppression reduced disease progression and complications associated with prostate cancer, there was no statistically significant difference in overall survival.<sup>31,32</sup> Likewise, the EORTC 30891 and Swiss Group for Clinical Cancer Research (SAKK) 08/88 studies demonstrated no difference in the prostate cancer-specific mortality rate, but the overall median time to onset of first symptoms from prostate cancer was improved in patients who received immediate ADT (compared to delayed treatment).<sup>33,34</sup> It is acknowledged that early use of ADT can potentially delay the development of metastatic disease and skeletal-related events, thus improving the patient's overall quality of life with respect to complications from the disease itself.<sup>35,36</sup> However, one must remember that early ADT use has not been shown to improve overall survival in this setting. Thus, the decision to pursue active surveillance versus ADT (either by medical or surgical castration) is influenced by other factors, such as the PSA doubling time, patient anxiety, and the long-term and short-term side effects of ADT.

### Factors That Influence Treatment Options

Because the timing of initiation of ADT is controversial, the key components that influence the consideration of

ADT are the rate of change of the PSA level (PSA doubling time), the patient's anxiety regarding his PSA level, and the side effects associated with ADT.

### **PSA Doubling Time**

PSA doubling time has primarily been used in the post-treatment setting as a predictor of prostate cancer–specific survival in men with biochemical recurrence.<sup>3,37,38</sup> Freedland and colleagues evaluated 5,096 patients who underwent radical prostatectomy to determine the predictive value of PSA doubling time in identifying patients who are at high risk for prostate cancer–specific mortality after biochemical recurrence.<sup>38</sup> They stratified patients into 4 categories of PSA doubling times: less than 3 months, 3–9 months, 9–15 months, and more than 15 months. The risk of prostate cancer–specific survival was very similar in patients with PSA doubling times greater than 9 months, and thus patients can be categorized into high, intermediate, and low risk for the development of clinical distant metastatic disease and mortality based on PSA doubling times of less than 3 months, 3–9 months, and more than 9 months.<sup>38</sup> Based on these statistics, a short PSA doubling time (<3 months) is associated with an increased risk of clinical progression, development of distant metastases, and prostate cancer–specific mortality.

### **Absolute Value of PSA Level**

One common question that is asked by patients is whether there is an absolute PSA value that would prompt the automatic initiation of ADT. Extrapolation from clinical trials evaluating intermittent ADT has defined an arbitrary range of 10–20 ng/mL.<sup>39,40</sup> However, there is no consensus opinion regarding the absolute value of PSA that would prompt initiation of therapy.

### **Patient Anxiety**

Patient anxiety plays an extremely important role in the decision-making process because significant anxiety negatively impacts quality of life, which is an important aspect of therapy. Although there are predictive factors for the development of metastatic disease, significant patient anxiety can encourage the use of certain therapies. For example, active surveillance does not expose patients to medication-associated side effects, but a constant fear of the unknown and potential development of metastatic disease can be as or more devastating than adverse events. Active engagement with the patient to discuss anxiety related to the diagnosis of recurrent disease can have a beneficial impact on quality of life, with referrals to health psychologists and discussion groups as ways to assist patients as they cope with this diagnosis.

## **Risks of ADT**

ADT, although relatively well tolerated as an anticancer treatment, carries significant side effects and toxicities for the older man, such as hot flashes, osteoporosis, erectile dysfunction, fatigue, weight gain, loss of muscle mass, and decline in cognitive function.<sup>41–43</sup> In addition, the side effects of ADT will increase with continued use over time due to prolonged androgen deprivation. These potential side effects negatively impact quality of life as patients become at risk for other complications, such as skeletal fractures from ADT-induced osteoporosis, metabolic syndrome, diabetes mellitus, and cardiovascular events. There is an unmet need to address the potential side effects of ADT and to use alternative approaches of ADT administration to minimize any negative impact on quality of life and yet effectively treat the biochemical recurrence.

## **Peripheral Androgen Blockade**

Because of the significant side effects associated with ADT, the use of peripheral androgen blockade was further evaluated as a means of antagonizing the actions of androgens without suppressing testosterone production, thus offering an improvement in quality of life.

Bicalutamide is approved as a monotherapy in Europe (150 mg/day) and Japan (80 mg/day), but it has not been approved by the US Food and Drug Administration (FDA).<sup>44,45</sup> In a trial from the Early Prostate Cancer program, bicalutamide at 150 mg/day significantly reduced the risk of objective progression (as defined by radiographic imaging) by 21% in comparison to placebo in locally advanced patients in a watchful waiting arm.<sup>46</sup> However, a subset analysis of patients with localized disease in the watchful waiting arm demonstrated that bicalutamide was associated with a trend in decreased survival. In the North American Trial 23, treatment with bicalutamide was not associated with a significant difference in PFS or overall survival among patients with stage M0 prostate cancer who had undergone radical prostatectomy or radiotherapy.<sup>47</sup> The results of this trial prevented the FDA approval of bicalutamide. It should be noted that the patient populations in these 2 studies differed; patients in the North American Trial 23 had already undergone primary treatment prior to enrollment, thus reflecting global differences in the overall management of prostate cancer.

As promising as single-agent bicalutamide is for reducing the risk of objective progression as compared to placebo, antiandrogen therapy alone has never been demonstrated to be superior to ADT.<sup>48,49</sup> Despite the purported benefits of maintaining testosterone levels and thus minimizing the side effects of castration, single-agent antiandrogen treatment still results in other toxicities and side effects, such as gynecomastia and mastodynia, which occurred in 74%

and 69% of patients, respectively. These side effects can be painful and are not necessarily an improvement when compared to the potential side effects of ADT.<sup>45</sup>

Single-agent bicalutamide as a monotherapy at 150 mg/day is not recommended and would not be considered a standard of care for treatment of prostate cancer. However, under rare circumstances, it can be considered a reasonable alternative in carefully selected patients who may not be able to tolerate ADT.

### Intermittent Approach of ADT

Intermittent ADT typically involves the administration of ADT in a cyclical fashion, with periods of ADT holidays in order to allow for the recovery of testosterone levels, thus minimizing the negative side effects of ADT. In patients who would be considered to benefit from ADT, the standard of care is continuous administration of ADT.<sup>50,51</sup> However, an intermittent approach is being used more frequently due to the purported benefits of reducing the potential toxicities associated with ADT while still maintaining PSA control.

In patients with metastatic or locally advanced disease, intermittent therapy has been demonstrated to be a feasible approach for treatment and is well tolerated when given for a minimum of 6 months and reinitiated when PSA levels rise to a range of 10–20 ng/mL.<sup>40</sup> The failure of the serum PSA to fall to normal levels during the initial induction ADT phase (within 32 weeks of ADT) is usually a sign of early progression to androgen independence, although this association has not been confirmed in randomized trials.<sup>40</sup> In fact, there are conflicting data regarding the benefits of intermittent ADT in delaying androgen independence.<sup>39,52</sup> At the very least, intermittent ADT in both phase II and phase III trials has been demonstrated to be tolerable and offers advantages in quality of life, including recovery of sexual function.<sup>53,54</sup> Although there might be an improvement in early side effects (eg, hot flashes, sexual dysfunction) with intermittent ADT, the data are inconclusive regarding any improvement in long-term side effects (eg, cardiovascular events, osteoporosis, obesity).<sup>55</sup>

SWOG 9346 is an international, collaborative phase III clinical trial evaluating intermittent ADT in patients with hormone-sensitive metastatic prostate cancer. Results were presented at the 2012 meeting of the American Society of Clinical Oncology. The trial demonstrated that intermittent ADT resulted in inferior survival when compared to continuous ADT.<sup>56</sup> There is a great amount of controversy regarding this conclusion, which was inferred based on the statistical definition of superiority and the lack of noninferiority. Nevertheless, if prostate cancer-specific survival is the main goal of therapy, then the results of SWOG 9346 would not support the use of intermittent ADT, and thus intermittent ADT would not be considered a standard of care for treatment of biochemically recurrent or metastatic disease.

It is also important to note that another co-primary endpoint of SWOG 9346 was quality of life. With intermittent ADT, men demonstrated improved sexual function, physical function, emotional function, and energy.<sup>57</sup> Because ADT can significantly impact a man's quality of life, it is an important issue to consider. Thus, in certain patients in whom quality of life is the primary consideration of therapy, it is possible to consider intermittent ADT.

The National Cancer Institute of Canada (NCIC) PR7 study is another phase III clinical trial evaluating intermittent versus continuous ADT in patients with biochemical recurrence but no evidence of metastatic disease.<sup>58</sup> Accrual is complete for this trial, and the results are pending.

### Clinical Trials

Given that there is no standard of care for the prostate cancer patient who develops biochemical recurrence, and the timing for initiation of ADT is poorly understood, these patients represent a rational population for the development of novel treatment approaches that may have fewer side effects than ADT. In addition, novel agents are being developed that may potentially delay the initiation of ADT. Currently, ongoing clinical trials for this population primarily use an immunotherapy approach. For instance, one clinical trial is evaluating pTVG-HP,<sup>59</sup> which is a DNA vaccine encoding prostate acid phosphatase, while another clinical trial is examining the vaccination of autologous dendritic cells loaded with Tn-MUC1 peptide.<sup>60</sup> For patients who are initiated on ADT, there are numerous clinical trials combining ADT with novel agents with the goal of improving the effect of ADT. For example, one particular trial evaluates a short course of ADT in combination with bevacizumab (Avastin, Genentech), in an attempt to reduce the side effects associated with ADT.<sup>61</sup> In patients with PSA recurrence only, there are clinical trials evaluating acai juice<sup>62</sup> and a supplement known as Prostate Health Cocktail, which contains vitamin D<sub>3</sub>, vitamin E, selenium, green tea extract, saw palmetto, lycopene, and soy derivatives.<sup>63</sup> Both of these studies use the specific endpoint of PSA response.

### Future Development of Clinical Trials

In this population of patients experiencing biochemical recurrence without radiographic evidence of metastasis, the unique aspect of conducting clinical trials is defining the proper endpoints for evaluation. The endpoint of any clinical trial is dependent on the overall goal of each novel agent. With the specific objective of achieving cure, a goal of overall survival and maintenance of an undetectable PSA level (PSA undetectable rate) would be appropriate. When the goal is to delay progression of disease and development of metastatic disease, primary endpoints should focus on time to events such as the development of radiographic metas-

tasis. In the development of novel anticancer agents for use in patients who have only PSA recurrence, it is necessary to consider other potential endpoints as surrogate markers of efficacy because these patients are typically asymptomatic and are in relatively good health. Although oncologists are typically interested in prolonging overall survival and delaying the development of metastatic disease, it is important that the side effects of potential therapy not have a negative impact on quality of life.

### Recommendations for Initiation of ADT

For those patients who continue to have biochemical recurrence in spite of local salvage therapies (or who may not be candidates for salvage therapies), we rely heavily on PSA doubling time as a good predictive marker of whether metastatic disease will develop. We acknowledge that other factors play a role in the decision-making process, but we typically follow these guidelines:

- Consideration of early ADT in those patients who have a PSA doubling time of less than 3 months, an absolute PSA level of greater than 20 ng/mL, a high Gleason score (8 or higher), and high-risk features, such as seminal vesicle invasion, extracapsular invasion, or positive margins.
- Continued active surveillance in patients with a PSA doubling time of greater than 10 months, a PSA level of less than 10 ng/mL, and no high-risk features.
- For those patients who have a PSA doubling time of 3–9 months, we have a lengthy discussion regarding the risks and benefits of early versus delayed ADT. We evaluate the patient's Gleason score, any high-risk surgical features from the prostatectomy, and the patient's anxiety level to develop a mutual consensus with him to determine the proper course of action. If the PSA doubling time decreases such that the PSA level is noted to rise more rapidly, we then initiate ADT at that time.

### Consideration of Intermittent ADT

We utilize intermittent ADT on a case-by-case basis. As a general rule, patients who have radiographic evidence of metastatic disease are not encouraged to pursue the intermittent approach because we believe the risks of developing complications from disease progression outweigh the benefits. For those patients with biochemical recurrence only, without any evidence of metastatic disease, we typically administer treatment until the PSA level reaches undetectable levels for a minimum duration of 9 months before consideration of an ADT-free holiday. In the rare instances where the PSA level is at a nadir but is still detectable, it is imperative that the patient is monitored closely for any signs of progression.

### Summary

The initial management of localized prostate cancer is focused on the use of therapies, such as prostatectomy or radiation therapy, with the goal of cure. Despite these interventions, a significant number of men will go on to develop biochemical recurrence of their disease. Careful consideration of adjuvant/salvage therapies must be given, especially in light of the known side effects of these treatments and the unknown impact on cancer-specific survival. For those men with persistent elevation in PSA, factors such as PSA doubling time can help the patient and clinician decide on the appropriate time to begin ADT. However, these discussions should include counseling regarding the risks and toxicities associated with ADT. Consideration for clinical trials is appropriate for this patient population, and many exciting therapies are emerging for patients with recurrent prostate cancer.

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